## Subpart K [Reserved]

## Subpart L—Alternative Procedures

### § 640.120 Alternative procedures.

(a) The Director, Center for Biologics Evaluation and Research, may issue 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. The Director may issue such an exception or alternative in response to:

(1) A written request from an establishment. Licensed establishments must submit such requests in accordance with § 601.12 of this chapter;

(2) An oral request from an establishment, if there are difficult circumstances and submission of a written request is not feasible. Establishments must follow up such oral request by submitting written requests under paragraph (a)(1) of this section within 5 working days.

(b) To respond to a public health need, the Director may issue a notice of 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, if a variance under this section is necessary to assure that blood, blood components, or blood products will be available in a specified location or locations to address an urgent and immediate need for blood, blood components, or blood products or to provide for appropriate donor screening and testing.

(c) If the Director issues such an exception or alternative orally, the Director will follow up by issuing a written notice of the exception or alternative. Periodically, FDA will provide a list of approved exceptions and alternative procedures on the FDA Center for Biologics Evaluation and Research Web site.

[80 FR 29906, May 22, 2015]

## Subpart M—Definitions and Medical Supervision

SOURCE: 80 FR 29906, May 22, 2015, unless otherwise noted.

### § 640.125 Definitions.

The definitions set out in § 630.3 of this chapter apply to the use of those defined terms in this part.

### § 640.130 Medical supervision.

The requirements for medical supervision established in § 630.5 of this chapter supplement the regulations in this part.

# 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 Eligibility of donor.
660.32 Collection of source material.
660.33 Testing of source material.
660.34 Processing.
660.35 Labeling.
660.36 Samples and protocols.

### Subpart E—Hepatitis B Surface Antigen

660.40 Hepatitis B Surface Antigen.
660.41 Processing.
660.43 Potency test.
660.44 Specificity.
660.45 Labeling.
660.46 Samples; protocols; official release.

### Subpart F—Anti-Human Globulin

660.50 Anti-Human Globulin.
660.51 Processing.
660.52 Reference preparations.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372; 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.* (1) In addition to the items required by other applicable labeling provisions of this subchapter, the following shall also be included:

(i) 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.

(ii) 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).

(iii) 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.

(iv) 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.

(v) The package shall include a package enclosure providing:

(A) Adequate instructions for use;

(B) A description of all recommended test methods; and

(C) Warnings as to possible hazards, including hepatitis, in handling the product and any ancillary reagents and materials accompanying the product.

(2) The applicant may provide the labeling information referenced in paragraph (c)(1) of this section in the form of:

(i) A symbol accompanied by explanatory text adjacent to the symbol;

(ii) A symbol not accompanied by adjacent explanatory text that:

(A) Is contained in a standard that FDA recognizes under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act;

(B) Is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition; and

(C) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used; or

(iii) A symbol not accompanied by adjacent explanatory text that:

(A) Is established in a standard developed by a standards development organization (SDO);

(B) Is not contained in a standard that is recognized by FDA under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act or is contained in a standard that is recognized by FDA but is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition;

(C) Is determined by the manufacturer to be likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the Federal Food, Drug, and Cosmetic Act;

(D) Is used according to the specifications for use of the symbol set forth in the SDO-developed standard; and

(E) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used.

(3) The use of symbols to provide the labeling information referenced in paragraph (c)(1) of this section which do not meet the requirements of paragraph (c)(2) of this section renders a device misbranded under section 502(c) of the Federal Food, Drug, and Cosmetic Act.

(4) For purposes of paragraph (c)(2) of this section:

(i) An SDO is an organization that is nationally or internationally recognized and that follows a process for standard development that is transparent, (*i.e.*, open to public scrutiny), where the participation is balanced, where an appeals process is included, where the standard is not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope.

(ii) The term ''symbols glossary'' means a compiled listing of:

(A) Each SDO-established symbol used in the labeling for the device;

(B) The title and designation number of the SDO-developed standard containing the symbol;

(C) The title of the symbol and its reference number, if any, in the standard; and

(D) The meaning or explanatory text for the symbol as provided in the FDA recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, the explanatory text as provided in the standard.

(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; 81 FR 38924, June 15, 2016]

### § 660.3 Reference panel.

A Reference Hepatitis B Surface Antigen Panel shall be obtained from the Food and Drug Administration, Center for Biologics Evaluation and Research, Reagents and Standards Shipping, 10903 New Hampshire Ave., Bldg. 75, Rm. G704, Silver Spring, MD 20993–0002 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; 70 FR 14985, Mar. 24, 2005; 80 FR 18093, Apr. 3, 2015]

### § 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 (see mailing addresses in § 600.2(c) of this chapter), 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) *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 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, 11014, Mar. 26, 1990; 70 FR 14985, Mar. 24, 2005; 80 FR 18093, Apr. 3, 2015]

## 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 containing one or more of the blood grouping antibodies listed in § 660.28(a)(4).

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

[53 FR 12764, Apr. 19, 1988, as amended at 65 FR 77499, Dec. 12, 2000; 81 FR 38925, June 15, 2016]

### § 660.21 Processing.

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

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

(3) A lot may be subdivided into sublots. If lots are to be subdivided, the manufacturer shall include this information in the biologics license application. The manufacturer shall describe the test specifications to verify that each sublot is identical to other sublots of the lot.

(4) Each lot of Blood Grouping Reagent shall be identified by a lot number. Each sublot shall be identified by that lot number to which a distinctive prefix or suffix shall be added. Final container and package labels shall bear the lot number and all distinctive prefixes and suffixes that have been applied to identify the sublot from which filling was accomplished.

(b) *Color coding of reagents.* Blood Grouping Reagents may be colored provided the added colorant does not adversely affect the safety, purity, or potency of the product and the colorant is approved by the Director, Center for Biologics Evaluation and Research.

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

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

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

[53 FR 12764, Apr. 19, 1988, as amended at 64 FR 56454, Oct. 20, 1999; 65 FR 77499, Dec. 12, 2000; 67 FR 9587, Mar. 4, 2002; 70 FR 14985, Mar. 24, 2005]

### § 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 Food and Drug Administration, Center for Biologics Evaluation and Research, Reagents and Standards Shipping, 10903 New Hampshire Ave., Bldg. 75, Rm. G704, Silver Spring, MD 20993–0002, and shall be used as described in the accompanying package insert for determining the potency of Blood Grouping Reagents.

[53 FR 12764, Apr. 19, 1988, as amended at 67 FR 9587, Mar. 4, 2002; 70 FR 14985, Mar. 24, 2005; 80 FR 18093, Apr. 3, 2015]

### § 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.

(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.

(1) For Anti-K, Anti-$\bar{k}$, 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.

[53 FR 12764, Apr. 19, 1988, as amended at 67 FR 9587, Mar. 4, 2002; 70 FR 14985, Mar. 24, 2005]

### § 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.

[53 FR 12764, Apr. 19, 1988, as amended at 67 FR 9587, Mar. 4, 2002; 70 FR 14985, Mar. 24, 2005]

### § 660.28 Labeling.

(a) 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:

(1) *Final container label*—(i) *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. 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. |

(ii) *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:

(A) Name of the antibody or antibodies present as set forth in paragraph (a)(4) of this section.

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

(C) Lot number, including sublot designations.

(D) Expiration date.

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

(F) Test method(s) recommended.

(G) Recommended storage temperature in degrees Celsius.

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

(I) 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.''

(iii) *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.

(iv) *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-$\bar{k}$, or Anti-$\bar{s}$.

(2) *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.

(i) Proper name of the product.

(ii) Name of the antibody or antibodies present as set forth in paragraph (a)(4) of this section.

(iii) Name, address (including ZIP Code), and license number of the manufacturer.

(iv) Lot number, including sublot designations.

(v) Expiration date.

(vi) Preservative used and its concentration.

(vii) Number of containers, if more than one.

(viii) Volume or equivalent volume for dried products when reconstituted, and precautions for adequate mixing when reconstituting.

(ix) Recommended storage temperature in degrees Celsius.

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

(xi) Reference to enclosed package insert.

(xii) If a dried product, a statement indicating the period within which the product may be used after reconstitution.

(xiii) The statement: ''FOR IN VITRO DIAGNOSTIC USE.''

(xiv) The statement: ''MEETS FDA POTENCY REQUIREMENTS.''

(xv) 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.''

(xvi) 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.

(3) *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.

(4) *Names of antibodies.*

BLOOD GROUP DESIGNATION FOR CONTAINER LABEL

| | |
|---|---|
| Anti-A | Anti-Jk$^{b}$ |
| Anti-$A_1$ | Anti-Js$^{a}$ |
| Anti-A, B | Anti-Js$^{b}$ |
| Anti-A and B | Anti-K |
| Anti-B | Anti-k |
| Anti-C | Anti-Kp$^{a}$ |
| Anti-C$^{w}$ | Anti-Kp$^{b}$ |
| Anti-$\bar{c}$ | Anti-Le$^{a}$ |
| Anti-CD | Anti-Le$^{b}$ |
| Anti-CDE | Anti-Lu$^{a}$ |
| Anti-Co$^{b}$ | Anti-Lu$^{b}$ |
| Anti-D | Anti-M |
| Anti-DE | Anti-M$^{g}$ |
| Anti-Di$^{a}$ | Anti-N |
| Anti-E | Anti-$P_1$ |
| Anti-e | Anti-S |
| Anti-Fy$^{a}$ | Anti-$\bar{s}$ |
| Anti-Fy$^{b}$ | Anti-U |
| Anti-I | Anti-Wr$^{a}$ |
| Anti-Jk$^{a}$ | Anti-Xg$^{a}$ |

(b) The applicant may provide the labeling information referenced in paragraph (a) of this section in the form of:

(1) A symbol accompanied by explanatory text adjacent to the symbol;

(2) A symbol not accompanied by adjacent explanatory text that:

(i) Is contained in a standard that FDA recognizes under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act;

(ii) Is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition; and

(iii) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used; or

(3) A symbol not accompanied by adjacent explanatory text that:

(i) Is established in a standard developed by a standards development organization (SDO);

(ii) Is not contained in a standard that is recognized by FDA under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act or is contained in a standard that is recognized by FDA but is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition;

(iii) Is determined by the manufacturer to be likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the Federal Food, Drug, and Cosmetic Act;

(iv) Is used according to the specifications for use of the symbol set forth in the SDO-developed standard; and

(v) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used.

(c) The use of symbols in device labeling to provide the labeling information referenced in paragraph (a) of this section which do not meet the requirements in paragraph (b) of this section renders a device misbranded under section 502(c) of the Federal Food, Drug, and Cosmetic Act.

(d) For purposes of paragraph (b) of this section:

(1) An SDO is an organization that is nationally or internationally recognized and that follows a process for standard development that is transparent, (*i.e.*, open to public scrutiny),

where the participation is balanced, where an appeals process is included, where the standard is not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope.

(2) The term ''symbols glossary'' means a compiled listing of:

(i) Each SDO-established symbol used in the labeling for the device;

(ii) The title and designation number of the SDO-developed standard containing the symbol;

(iii) The title of the symbol and its reference number, if any, in the standard; and

(iv) The meaning or explanatory text for the symbol as provided in the FDA recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, the explanatory text as provided in the standard.

[81 FR 38925, June 15, 2016]

## Subpart D—Reagent Red Blood Cells

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

### § 660.30 Reagent Red Blood Cells.

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

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

[52 FR 37450, Oct. 7, 1987, as amended at 64 FR 56454, Oct. 20, 1999]

### § 660.31 Eligibility of donor.

Donors of peripheral blood for Reagent Red Blood Cells must meet all the criteria for donor eligibility under §§ 630.10 and 630.15 of this chapter.

[80 FR 29906, May 22, 2015]

### § 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 biologics license application. Group O Reagent Red Blood Cells used in the detection or identification of unexpected antibodies shall include at least the following common antigens in each lot of the product: D, C, E, $\bar{c}$, e, K, $\bar{k}$, $Fy^a$, $Fy^b$, $Jk^a$, $Jk^b$, $Le^a$, $Le^b$, $P_1$, M, N, S, and $\bar{s}$.

[52 FR 37450, Oct. 7, 1987, as amended at 55 FR 11013, Mar. 26, 1990; 64 FR 56454, Oct. 20, 1999]

### § 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.

[52 FR 37450, Oct. 7, 1987, as amended at 55 FR 11013, Mar. 26, 1990; 67 FR 9587, Mar. 4, 2002]

### § 660.35 Labeling.

(a) 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:

(1)(i) 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.

(ii) 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.

(2) 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''.

(3) 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.

(4) 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 pre-transfusion tests, done in lieu of a major crossmatch, to detect unexpected antibodies in patients' samples.

(5) 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.

(6) 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.

(7) 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.

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

(9) 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.

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

(11) 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.''

(12) 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.

(13) 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.

(b) The applicant may provide the labeling information referenced in paragraph (a) of this section in the form of:

(1) A symbol accompanied by explanatory text adjacent to the symbol;

(2) A symbol not accompanied by adjacent explanatory text that:

(i) Is contained in a standard that FDA recognizes under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act;

(ii) Is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition; and

(iii) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used; or

(3) A symbol not accompanied by adjacent explanatory text that:

(i) Is established in a standard developed by a standards development organization (SDO);

(ii) Is not contained in a standard that is recognized by FDA under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act or is contained in a standard that is recognized by FDA but is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition;

(iii) Is determined by the manufacturer to be likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the Federal Food, Drug, and Cosmetic Act;

(iv) Is used according to the specifications for use of the symbol set forth in the SDO-developed standard; and

(v) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used.

(c) The use of symbols in device labeling to provide the labeling information referenced in paragraph (a) of this section which do not meet the requirements of paragraph (b) of this section renders a device misbranded under section 502(c) of the Federal Food, Drug, and Cosmetic Act.

(d) For purposes of paragraph (b) of this section:

(1) An SDO is an organization that is nationally or internationally recognized and that follows a process for standard development that is transparent, (*i.e.*, open to public scrutiny), where the participation is balanced, where an appeals process is included, where the standard is not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope.

(2) The term ''symbols glossary'' means a compiled listing of:

(i) Each SDO-established symbol used in the labeling for the device;

(ii) The title and designation number of the SDO-developed standard containing the symbol;

(iii) The title of the symbol and its reference number, if any, in the standard; and

(iv) The meaning or explanatory text for the symbol as provided in the FDA recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, the explanatory text as provided in the standard.

[81 FR 38926, June 15, 2016]

### § 660.36 Samples and protocols.

(a) The following shall be submitted to the Center for Biologics Evaluation and Research Sample Custodian (see mailing addresses in § 600.2(c) of this chapter), 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 (see mailing addresses in § 600.2(c) of this chapter), 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 (see mailing addresses in § 600.2(c) of this chapter). The sample should contain a

minimum volume of 0.5 milliliter of red blood cells.

[52 FR 37450, Oct. 7, 1987, as amended at 55 FR 11013, 11015, Mar. 26, 1990; 67 FR 9587, Mar. 4, 2002; 70 FR 14985, Mar. 24, 2005; 80 FR 18093, Apr. 3, 2015]

## 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]

### § 660.43 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.

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

(1) 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.

(2) 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).

(3) 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.

(4) The package shall include a package insert providing:

(i) Detailed instructions for use,

(ii) An adequate description of all recommended test methods, and

(iii) Warnings as to possible hazards, including hepatitis transmitted in handling the product and any ancillary reagents and materials accompanying the product.

(b) The applicant may provide the labeling information referenced in paragraph (a) of this section in the form of:

(1) A symbol accompanied by explanatory text adjacent to the symbol;

(2) A symbol not accompanied by adjacent explanatory text that:

(i) Is contained in a standard that FDA recognizes under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act;

(ii) Is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition; and

(iii) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used; or

(3) A symbol not accompanied by adjacent explanatory text that:

(i) Is established in a standard developed by a standards development organization (SDO);

(ii) Is not contained in a standard that is recognized by FDA under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act or is contained in a standard that is recognized by FDA but is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition;

(iii) Is determined by the manufacturer to be likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the Federal Food, Drug, and Cosmetic Act;

(iv) Is used according to the specifications for use of the symbol set forth in the SDO-developed standard; and

(v) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used.

(c) The use of symbols in device labeling to provide the labeling information referenced in paragraph (a) of this section which do not meet the requirements of paragraph (b) of this section renders a device misbranded under section 502(c) of the Federal Food, Drug, and Cosmetic Act.

(d) For purposes of paragraph (b) of this section:

(1) An SDO is an organization that is nationally or internationally recognized and that follows a process for standard development that is transparent, (*i.e.,* open to public scrutiny), where the participation is balanced, where an appeals process is included, where the standard is not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope.

(2) The term ''symbols glossary'' means a compiled listing of:

(i) Each SDO-established symbol used in the labeling for the device;

(ii) The title and designation number of the SDO-developed standard containing the symbol;

(iii) The title of the symbol and its reference number, if any, in the standard; and

(iv) The meaning or explanatory text for the symbol as provided in the FDA

recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, the explanatory text as provided in the standard.

[81 FR 38928, June 15, 2016]

### § 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 (see mailing addresses in § 600.2(c) of this chapter), 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, 11014, Mar. 26, 1990; 70 FR 14985, Mar. 24, 2005; 80 FR 18093, Apr. 3, 2015]

## 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(a)(4).

(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, as amended at 65 FR 77499, Dec. 12, 2000; 81 FR 38928, June 15, 2016]

### § 660.51 Processing.

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

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

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

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

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

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

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

[50 FR 5579, Feb. 11, 1985, as amended at 50 FR 16474, Apr. 26, 1985; 65 FR 77499, Dec. 12, 2000; 67 FR 9587, Mar. 4, 2002]

### § 660.52 Reference preparations.

Reference Anti-Human Globulin preparations shall be obtained from the Food and Drug Administration, Center for Biologics Evaluation and Research, Reagents and Standards Shipping, 10903 New Hampshire Ave., Bldg. 75, Rm. G704, Silver Spring, MD 20993–0002, and shall be used as described in the accompanying package insert for determining the potency of Anti-Human Globulin.

[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; 67 FR 9587, Mar. 4, 2002; 70 FR 14986, Mar. 24, 2005; 80 FR 18093, Apr. 3, 2015]

### § 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.

[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; 67 FR 9587, Mar. 4, 2002; 70 FR 14986, Mar. 24, 2005]

### § 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:

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

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

[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; 67 FR 9587, Mar. 4, 2002; 70 FR 14986, Mar. 24, 2005]

**§ 660.55 Labeling.**

(a) 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:

(1) *Final container label*—(i) *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.

(ii) *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:

(A) Name of the antibody or antibodies present as set forth in paragraph (a)(4) 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.

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

(C) Lot number, including any sublot designations.

(D) Expiration date.

(E) Source of the product.

(F) Recommended storage temperature in degrees Celsius.

(G) Volume of product.

(H) 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.''

(I) If the final container is not enclosed in a package, all items required for a package label shall appear on the container label.

(iii) *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. The prefix anti- and other parts of the name such as polyspecific may appear in smaller type.

(iv) *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.

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

(i) Proper name of the product, and the name of the antibody or antibodies as listed in paragraph (a)(4) of this section.

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

(iii) Lot number, including any sublot designations.

(iv) Expiration date.

(v) Preservative(s) used and its concentration.

(vi) Number of containers, if more than one.

(vii) Recommended storage temperature in degrees Celsius.

(viii) Source of the product.

(ix) Reference to enclosed package insert.

(x) The statement: ''For In Vitro Diagnostic Use.''

(xi) The statement: ''Meets FDA Potency Requirements.''

(xii) 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.

(xiii) Appropriate cautions.

(3) *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.

(4) *Names of antibodies.* Anti-Human Globulin preparations may contain one or more of the antibody specificities listed in this paragraph as described in paragraph (a)(1)(ii)(A) of this section.

| 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. |

(b) The applicant may provide the labeling information referenced in this section in the form of:

(1) A symbol accompanied by explanatory text adjacent to the symbol;

(2) A symbol not accompanied by adjacent explanatory text that:

(i) Is contained in a standard that FDA recognizes under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act;

(ii) Is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition; and

(iii) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used; or

(3) A symbol not accompanied by adjacent explanatory text that:

(i) Is established in a standard developed by a standards development organization (SDO);

(ii) Is not contained in a standard that is recognized by FDA under its authority in section 514(c) or is contained in a standard that is recognized by FDA but is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition;

(iii) Is determined by the manufacturer to be likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the Federal Food, Drug, and Cosmetic Act;

(iv) Is used according to the specifications for use of the symbol set forth in the SDO-developed standard; and

(v) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used.

(c) The use of symbols in device labeling to provide the labeling information referenced in paragraph (a) of this section which do not meet the requirements of paragraph (b) of this section renders a device misbranded under section 502(c) of the Federal Food, Drug, and Cosmetic Act.

(d) For purposes of paragraph (b) of this section:

(1) An SDO is an organization that is nationally or internationally recognized and that follows a process for

standard development that is transparent, (*i.e.*, open to public scrutiny), where the participation is balanced, where an appeals process is included, where the standard is not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope.

(2) The term ''symbols glossary'' means a compiled listing of:

(i) Each SDO-established symbol used in the labeling for the device;

(ii) The title and designation number of the SDO-developed standard containing the symbol;

(iii) The title of the symbol and its reference number, if any, in the standard; and

(iv) The meaning or explanatory text for the symbol as provided in the FDA recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, the explanatory text as provided in the standard.

[81 FR 38928, June 15, 2016]

# PART 680—ADDITIONAL STANDARDS FOR MISCELLANEOUS PRODUCTS

Sec.



AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 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.

## § 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 (see mailing address in § 600.2(a) of this chapter).

(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.