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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Certifier J. COOKE

Food and Drug Administration

[Docket No. 2004N-0367]

**Cumulative List of Exceptions and Alternative Procedures Approved by the Director of the Center for Biologics Evaluation and Research**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability a cumulative list of exceptions and alternative procedures to requirements regarding blood, blood components, and blood products that have been approved by the Director of the Center for Biologics Evaluation and Research (CBER). Also, FDA is announcing that this list is posted on the Internet and it will be periodically updated.

**ADDRESSES:** Copies of the cumulative list of exceptions and alternative procedures are available from the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and the Office of Communication, Training and Manufacturers Assistance (HFM-40), Food and Drug Administration, suite 200 N, 1401 Rockville Pike, Rockville, MD 20852-1448, 1-800-835-4709 or 301-827-1800. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the cumulative list of exceptions and alternative procedures.

**FOR FURTHER INFORMATION CONTACT:** Nathaniel L. Geary, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, suite 200N, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-6210.

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**SUPPLEMENTARY INFORMATION:****I. Background**

The Director of CBER has approved exceptions or alternative procedures that have been requested by blood establishments under § 640.120 (21 CFR 640.120). Section 640.120 grants the Director authority to approve exceptions or alternatives to any requirement in subchapter F (Biologics) of chapter I, parts 600 through 680 (21 CFR parts 600 through 680) regarding blood, blood components, or blood products.

FDA is announcing publication of a cumulative list of exceptions and alternative procedures to requirements regarding blood, blood components, and blood products that have been approved by the Director of CBER. Also, FDA is announcing that this list is posted on the Internet and it will be periodically updated.

**II. List of Approved Exceptions and Alternative Procedures (§ 640.120(b))****§ 600.15(a)**

- Allow use of autologous units that were transported in a shipping container without ice and exposed to temperatures of 10.0 °C to 10.5 °C for 10 minutes.

**§ 606.60(b)**

- Calibrate digital thermometer according to the schedule recommended by manufacturer, instead of monthly as required by regulation.

**§ 606.65(e)**

- Deviate from manufacturer's instructions to use the Gen-Probe Procleix HIV-1/HCV Assay and Roche COBAS Ampliscreen HIV-1 and HCV nucleic

acid tests on whole blood, red blood cells (RBC), platelets, source leukocytes, therapeutic exchange plasma, and recovered plasma intended for further manufacturing.

- Deviate from manufacturer's instruction to use samples containing up to 200 milligrams (mg)/deciliters (dL) hemoglobin or 800 mg/dL triglycerides in the following assays: Abbott HIV AB HIV-1/HIV-2, (rDNA) EIA (LN3A77), Ortho Hepatitis B Core Antibody, Ortho Hepatitis B Surface Antigen ELISA System 2, and Roche Alanine Aminotransferase.

- Deviate from manufacturer's instruction to use an alternate testing algorithm for confirming repeatedly reactive HIV-1 p24 antigen test results. Specifically, a licensed HIV-1 single unit Nucleic Acid Test will be performed in place of the HIV-1 p24 antigen neutralization test and the results used for donor notification and counseling and recipient tracing.

- Deviate from manufacturer's instructions to test donor specimens that were initially reactive using Ortho HbsAg System 3, in duplicate using Genetic Systems HbsAg EIA 3.0 (shaker method). If either or both of the donor samples test reactive using Genetic Systems HbsAg EIA 3.0 (shaker method), the donor specimen will be tested using Genetic Systems HbsAg Confirmatory 3.0 (shaker method).

#### **§ 606.121**

- Use of full face green labels for autologous use only units.
- Use of black print for all statements on container labels (omit use of statements in red print.) (Regulation revised—variance request no longer needed.)
- Use of "Autologous" on label in lieu of "Paid" or "Volunteer"

- Omit special labeling from RBC with positive antibody screens that are suspended in additive solution, if the supernatant of the additive solution was tested using approved methods and found to be negative for unexpected antibodies.

- Place ABO/Rh label and “Donor Untested” on group and type label position.

- Print the anticoagulant name after the proper product name instead of preceding it. (Done for ISBT 128 labels.)

#### **§ 606.122(m)**

- Extend the storage time of thawed Fresh Frozen Plasma (FFP) at 1 to 6 °C to 24 hours, instead of 6 hours.

#### **§ 606.151**

- Omit performing a minor side crossmatch on RBC prepared in additive solutions that have not been screened for unexpected antibodies.

- Use of a computer (electronic) crossmatch instead of a major side crossmatch. (Regulation revised—variance request no longer needed.)

- Use of a type and screen procedure as an alternative method for the antiglobulin crossmatch. (Regulation revised—variance request no longer needed.)

- Allow use of a recipient sample up to 72 hours old for pre-transfusion testing. (Regulation revised—variance request no longer needed.)

#### **§ 610.40**

- Ship source leukocytes to the manufacturer before infectious disease testing has been completed, provided the product is labeled that testing is not complete and stored in quarantine until the manufacturer has received the test results. (Regulation revised—variance request no longer needed.)

- Ship autologous blood unit to another establishment without testing unit for communicable disease agents. Testing performed on sample drawn on subsequent donation.

- Ship autologous blood unit to another establishment for processing and labeling and return to collecting facility without testing unit for communicable disease agents, provided neither facility has a crossover policy.

- Allow shipment under quarantine of untested source plasma labeled as tested negative, to warehouse operated by another manufacturer for storage until testing is completed.

- Reinstate one donor with nondiscriminated results (NDR) on the Procleix HIV-1/HCV assay provided the donor tests negative for HIV RNA and HCV RNA using the Procleix Discriminatory assays and anti-HIV 1/2 using Genetic Systems EIA.

- Allow shipment under quarantine of source plasma before completion of PCR testing, and labeled as pending NAT, to another licensed manufacturer who will cull and destroy NAT reactive units under a contractual arrangement with the source plasma manufacturer.

- Allow shipment under quarantine of source plasma that is labeled as negative/nonreactive for infectious diseases before completion of the infectious disease tests, to a contract off-site storage facility not operating under a U.S. license. source plasma manufacturer will cull and destroy reactive units according to their standard procedures.

### **§ 610.53**

- Extend CPD and CP2D liquid plasma expiration date to 42 days when stored at 1 to 6 °C.

- Allow use of 53 vials of deglycerolized immunogen RBC that were exposed to temperatures from 6 to 8 °C for up to 3 hours.

**§ 640.3**

- Allow whole blood collection from autologous donors who don't meet donor suitability requirements.

- Allow whole blood collection from donors with a history of hepatitis before age 11. (Regulation revised—variance request no longer needed.)

- Allow 4-week intervals between FFP donations when it is collected as a by-product of a plateletpheresis procedure.

- Allow individuals with hereditary hemochromatosis to donate blood and blood components more frequently than every 8 weeks without examination or certification of health by physician at time of donation and to be exempt from placing special labeling about the donor's disease on the blood components.

- Allow post-donation requalification after day of donation of donors who used an outdated vCJD donor questionnaire.

**§§ 640.4(h) and 640.11(a)**

- Allow use of whole blood and RBC that have been exposed to temperatures up to 11.5 °C for 4.5 hours or 17 °C for 2 hours and 15 minutes, provided that the safety, purity, and potency were not affected.

**§ 640.5**

- Allow syphilis testing to be performed on 27 donors on a substitute sample drawn after day of donation.

- Allow specimens used for NAT assay to be collected up to 24 hours prior to the collection of heparinized whole blood units.

**§ 640.11(a)**

- Allow use of RBC and RBC Leukocyte-Reduced that were stored at 1 °C to -3 °C for up to 4 hours, provided each unit was examined for hemolysis before distribution.

- Allow use of RBC that were exposed to temperatures between 6 °C and 10.5 °C for up to 4.75 hours, provided each unit was examined for hemolysis before distribution.

**§ 640.23(b)**

- Allow ABO and Rh testing on plateletpheresis donors to be performed every 90 days.

**§ 640.32(b)**

- Relabel FFP collected by apheresis as recovered plasma prior to expiration of the original product. (Done to manage FFP inventory collected during periods of increased risk for West Nile Virus.)

**§ 640.34**

- Allow use of A and AB FFP that was warmed to -4 °C over an 18-hour time period, provided that safety, purity, and potency were not affected and the consignee is notified of the temperature deviation. Relabeling or shortening of the expiration date is not required.

- Allow plasma manufactured from whole blood to be frozen within 24 hours after phlebotomy. Blood component must be labeled as “PLASMA Frozen within 24 hours after Phlebotomy.”

- Allow use of 45 units of FFP that were exposed to temperatures between -6 °C and -18 °C for a total of 4.5 hours, provided the blood components remained frozen during the whole time period.

- Allow distribution of 1,201 units of FFP and 395 units of Plasma Cryoprecipitate Reduced that were exposed to temperatures between -16.4 °C

and -18 °C for a total of 1.5 hours, provided the blood components remained frozen during the whole time period.

**§§ 640.34 and 640.54(a)**

- Allow distribution of 1,235 units of FFP and 963 units of Plasma Cryoprecipitate Reduced and prepare Cryoprecipitated AHF from 1,531 units Cryoprecipitate rich plasma that were exposed to temperatures between -11.8 °C and -18 °C for a total of 5.5 hours, provided the blood components remained frozen during the whole time period.

**§§ 640.61, 640.62, and 640.63**

- Permit trained staff to explain the hazards of plasmapheresis and obtain informed consent.

- Allow physician substitutes to perform some of the duties of a physician (i.e., physical examinations of source plasma donors) and to approve physician substitute training programs.

**§ 640.63**

- Draw one donor with a rare RBC antibody who was Anti-HCV positive.
- Draw a donor with IgM Anti-HAV with a disease state program approval.
- Allow plasmapheresis of an asymptomatic donor with a history of Lyme Disease, provided product is labeled that it was collected from donor with a history of Lyme Disease.

- Allow a donor with a slightly abnormal Serum Protein Electrophoresis (SPE) to donate for an Infant Botulism Program.

- Allow individuals with childhood history of hepatitis at age 10 or younger to donate. (Regulation revised—variance request no longer needed.)

- Allow source plasma to be collected from a specific anti-e donor whose weight fluctuates between 108 and 112 pounds (lbs) to donate, provided the

weight does not drop below 108 lbs at time of donation and donor meets all other eligibility requirements.

**§ 640.65**

- Allow an infrequent plasmapheresis program in source plasma facilities. Donors may donate without a physical examination or SPE.

- Allow collection of source plasma from anti-HCV reactive donors with elevated SPE results (no more than 25 percent over normal limits established by testing lab), provided the donor's personal physician has given written approval.

**§ 640.66**

- Allow a physician substitute to schedule Tetanus Toxoid injections and review responses of donors immunized with licensed vaccines. The center physician must still do weekly evaluation of records.

**§ 640.76**

- Allow source plasma exposed to more than one episode of storage temperature fluctuations warmer than -20 °C and colder than -5 °C for less than 72 total hours to not be relabeled as "Source Plasma, Salvaged," provided the plasma was not allowed to thaw and the consignee is notified of the temperature deviations.

- Allow a revised procedure for labeling shipments of Source Plasma, Salvaged. Instead of labeling each unit, the facility may mark "Source Plasma, Salvaged" on the shipping cartons and packing slips.

- Allow 600 liters of source plasma stored at temperatures ranging from -20 °C to +19 °C for 3 1/2 hours to be relabeled as "Source Plasma, Salvaged."

- Allow 53 units of source plasma intended for further manufacture into injectable products, that were stored at 14 °C to be relabeled for further

manufacture into noninjectable products, provided that label states that it was stored at 14 °C.

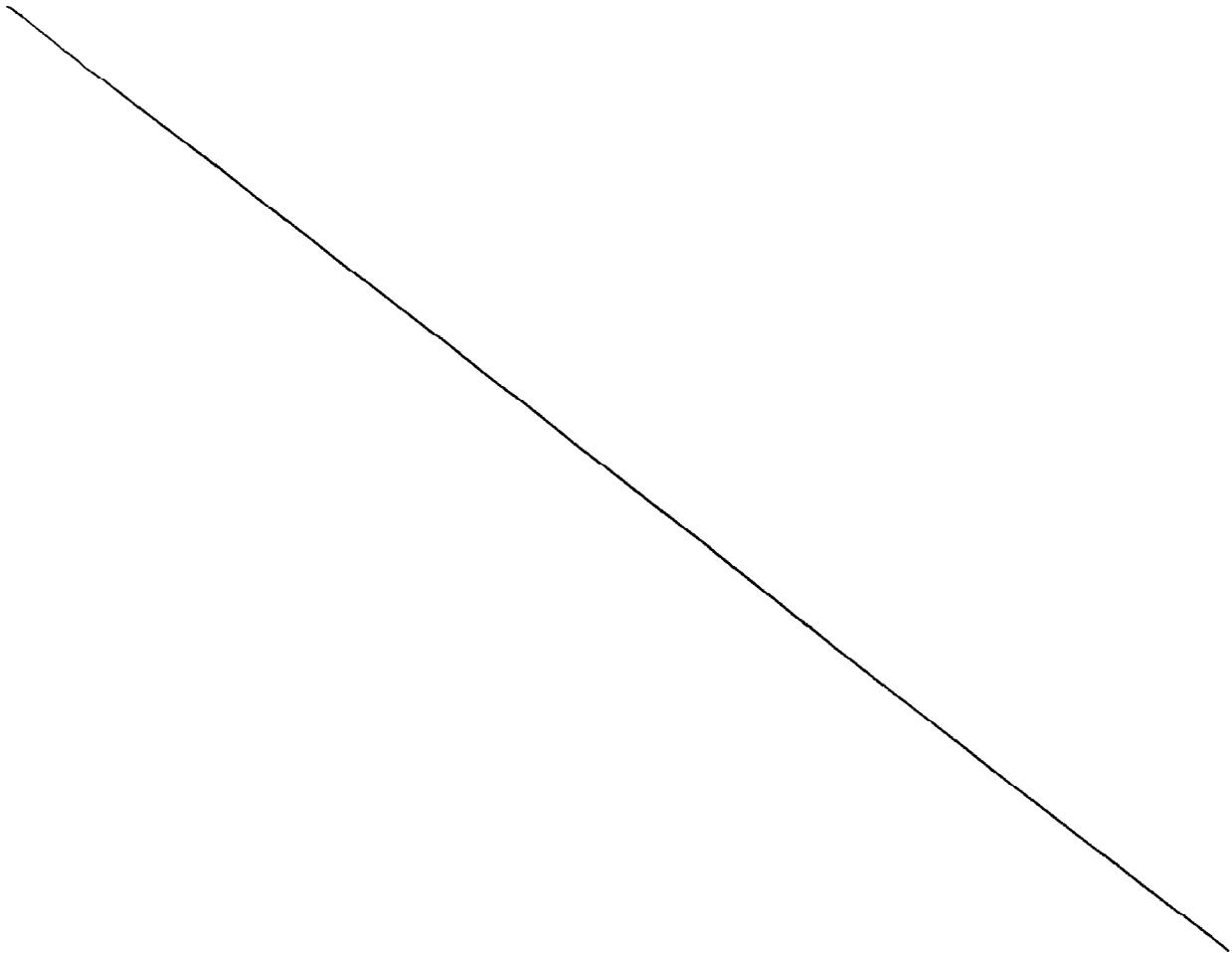
**§§ 660.22 and 660.28**

- Use FTA–ABS methodology as an alternative procedure to quantitative RPR testing on samples with a qualitative reactive RPR test for syphilis.

- Use an alternate procedure to perform FDA required tests for lot release action on bulk product prior to filling final containers for RBC antigen phenotyping reagents and Anti-Human Globulin reagents.

**§ 660.28**

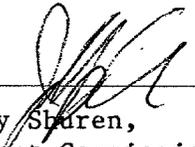
- Allow the use of existing labels for blood grouping reagents, pending reprinting of corrected labels.



**III. Electronic Access**

Persons with access to the Internet may obtain the cumulative list of exceptions and alternative procedures at <http://www.fda.gov/cber/blood/exceptions.htm>.

Dated: 9/20/04  
September 20, 2004.

  
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Jeffrey Shuren,  
Assistant Commissioner for Policy.

  
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