

May 12, 2023

## **Exceptions and Alternative Procedures Approved Under 21 CFR 640.120(a)**

Under title 21 of the Code of Federal Regulations 640.120(a), the Director, Center for Biologics Evaluation and Research, may issue an exception or alternative to any requirement in subchapter F (Biologics, Parts 600-680) of Chapter I (Food and Drug Administration, Department of Health and Human Services) of title 21 of the Code of Federal Regulations regarding blood, blood components or blood products.

Both licensed and unlicensed blood establishments must submit requests for an exception or alternative to the requirements in Parts 600-680. Licensed establishments must submit the request in accordance with 21 CFR 601.12 and may reference our guidance document entitled: [Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture \(December 2014\)](#).

Requests for such exceptions or alternative procedures should be made in writing; however, if there are difficult circumstances and submission of a written request is not feasible, such requests may be made orally, followed by a written request within 5 working days. If the Director issues an exception or alternative orally, the Director will follow up with a written notice.

It should be noted that requests for exceptions or alternatives to the regulations include specific circumstances and may require submission of supporting data unique to the circumstance. Publication of this list does not necessarily mean that the exceptions or alternatives can be generally applied to other manufacturers.

### **The following exceptions or alternative procedures have been approved under 21 CFR 640.120(a) during January 2023 – March 2023.**

**1. 606.65(e) & 610.53(b)**

To manufacture Apheresis Platelets, Leukocytes Reduced (single, double, and triple collections) suspended in 100% plasma, stored at 1-6 °C for up to 14 days without agitation. The cold stored platelets products will be used to treat actively bleeding patients through day 14 of storage when conventional platelet products are unavailable, or their use is not practical.

**2. 630.30(b)(1) & 630.15(b)(6)(iii)**

One-time exception to release Source Plasma donations collected from donors who had exceeded the Red Blood Cell loss limit and should have been deferred under 21 CFR 630.15(b)(6)(iii).

**3. 630.30(b)(1) & 640.65(b)(1)(i)**

One-time exception to distribute Source Plasma units collected from donors who did not have a serum protein electrophoresis (SPE) and serological test for syphilis (STS) performed on their initial physical examination or plasmapheresis, provided the units are released as follows:

- The units collected from donors who had a follow-up SPE/STS sample tested with acceptable results may be used for further manufacturing into injectable

products.

- The units collected from donors who did not have a follow-up SPE/STS sample tested may be used for further manufacturing into non-injectable products.

**4. 640.54(a)(2) & 606.65(e)**

To manufacture Cryoprecipitated AHF and Pooled Cryoprecipitated AHF from Plasma Frozen Within 24 Hours After Phlebotomy (PF24).

**5. 640.76(a)(1)**

- a. One-time exception to allow Source Plasma units intended for further manufacturing into injectable products to not be relabeled as "Source Plasma Salvaged". The units were exposed to more than one episode of storage temperature fluctuations warmer than -20 °C and colder than +10 °C for approximately 5 hours and remained frozen solid. In addition, the consignee will be notified of the temperature deviation.
- b. One-time exception to allow Source Plasma units intended for further manufacturing into injectable products to not be relabeled as "Source Plasma Salvaged". The units were exposed to storage temperature fluctuations warmer than -20 °C and colder than +10 °C for approximately 2 hours and 30 minutes and remained frozen solid. In addition, the consignee will be notified of the temperature deviation.

**6. 640.76(b)**

One-time exception to allow Source Plasma units intended for further manufacturing into injectable products to not be relabeled as "Source Plasma Salvaged". The units were exposed to shipping temperature fluctuations warmer than -5 °C and colder than +10 °C for approximately 14 hours and 30 minutes and remained frozen solid. In addition, the consignee will be notified of the temperature deviation.

**The following is a cumulative list of all exceptions or alternative procedures approved under 21 CFR 640.120 (a) to the current requirements in 21 CFR Part 600-680.**

**1. 21 CFR 600.15(a):**

- a. Allow use of autologous units that were transported in a shipping container without ice and exposed to temperature of 10.0 °C to 10.5 °C for 10 minutes.
- b. Allow use of multi-antigen typed units designated for patients with multiple antibodies that were exposed to temperatures between 10 °C and 12 °C during delayed transport during Hurricane Rita, provided the units were packed on ice immediately after removal from the 1 °C to 6 °C controlled storage prior to shipment.
- c. Allow distribution of Platelets, Pheresis products that were exposed to temperatures colder than 20 °C during shipment, provided the pH and visual inspection of the products performed prior to distribution were acceptable and the transfusion facilities receiving the products were notified of the temperature excursion.
- d. Allow distribution of Platelets, Pheresis that were exposed to temperatures cooler than 20 °C during shipment, provided (1) the units were inspected both upon receipt and before distribution to the transfusion services, (2) the transfusion services are informed of the temperature excursion, and (3) the blood center will monitor any reports of adverse events relating to the units involved in the incident.

- e. To release for transfusion 7 group AB Fresh Frozen Plasma units that were shipped at -12 °C. The approval was granted for the following reasons: (1) the units will be used to support a specific patient whose needs could not be met by the current Fresh Frozen Plasma inventory; (2) the units were still frozen upon receipt and there was no evidence of thawing during shipment; (3) the shipping facility was notified and stated they would investigate this event and implement appropriate corrective actions; and (4) the transfusion service medical director approved the use of the units.
- f. To administer a Red Blood Cell unit that was transported and the temperature upon receipt was 14 °C. The approval was based on the following information: 1) the unit is rare (Rh negative, Cellano negative) and the patient requires transfusion therapy with Red Blood Cells; 2) the transfusion service notified the shipping facility; 3) the transfusion service visually inspected the unit and there was no evidence of hemolysis or clumping; 4) the unit was cultured and it was negative for both Gram negative and Gram positive organisms and 5) the transfusion service medical director approved the use of the unit.
- g. To release for transfusion 27 Red Blood Cell units collected from Whole Blood that were exposed to storage temperature of 12.4 °C for approximately 5 hours upon receipt.
- h. To release for transfusion 7 Apheresis Platelet units that were exposed to temperatures colder than 20 °C (16 °C and 17 °C) during shipment.

**2. 21 CFR 601.12(e):**

Allow distribution of Red Blood Cells, Leukocytes Reduced, collected with the Haemonetics MCS+ LN 8150 using a revised comparability protocol before the comparability protocol has been submitted and approved by FDA. The comparability protocol must be revised because the instrument collection sets were modified to include the same filter (832 F) as an inline filter, but there is no change in the final product.

**3. 21 CFR 606.60(b):**

- a. Calibrate the Traceable Memory Monitoring Thermometer quarterly, instead of monthly as required by regulation. The thermometer's package insert did not include recommendations for frequency of calibration; therefore, approval was based on review of submitted data.
- b. Calibrate the Traceable Memory Monitoring Thermometer, the Traceable Sentry Thermometer Centigrade Thermometer and the Traceable Big-Digit Memory Thermometer annually, instead of monthly as required by regulation. The thermometer's package insert did not include recommendations for frequency of calibration; therefore, approval was based on review of submitted data.
- c. To not standardize the HemoCue Hb 201+ hemoglobinometer against a cyanmethemoglobin standard each day of use, provided the hemoglobinometer is checked each day of use using appropriate whole blood, hemolysate, or other validated hematology controls in addition to the internal self-test of the optronic unit.
- d. Calibrate electronic digital thermometer bi-annually instead of monthly. The thermometer's package insert did not include recommendations for frequency of calibration; therefore, approval was based on review of submitted data.
- e. To distribute 31 Whole Blood units that were weighed on a blood container scale that had not been standardized against a known weight on the day of use.
- f. To distribute blood components prepared from Whole Blood units that were processed in refrigerated centrifuges that had not undergone routine daily control (RPM and temperature) on the day of use.
- g. To discontinue comparing temperature chart recorders against calibrated thermometers on a daily basis, and to perform calibration of the electronic temperature monitoring system at 12-month intervals.

h. To calibrate the digital electronic thermometer annually instead of monthly.

**4. 21 CFR 606.60(b) & 606.160(b)(5)(ii):**

To distribute units collected from 2 donors who were screened using a Hemocue Hb System for which there were no records of the daily performance check performed before the instrument was used. The approval was granted because the performance checks performed the day before and the day after were acceptable.

**5. 21 CFR 606.65(e):**

- a. 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, Platelets, Source Leukocytes, Therapeutic Exchange Plasma and Recovered Plasma intended for further manufacturing.
- b. Deviate from manufacturer's instruction to use samples containing up to 200 mg/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 ELISA, Ortho Hepatitis B Surface Antigen ELISA System 2, and Roche Alanine Aminotransferase.
- c. 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.
- d. 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, Platelets, Source Leukocytes, Therapeutic Exchange Plasma and Recovered Plasma intended for further manufacturing.
- e. Deviate from manufacturer's instruction to use samples containing up to 200 mg/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 ELISA, Ortho Hepatitis B Surface Antigen ELISA System 2, and Roche Alanine Aminotransferase.
- f. 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.
- g. 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).
- h. Deviate from the testing algorithm described in the manufacturer's instructions for performing duplicate testing on an initially reactive specimen because of a software bug resulting in user lock-out or an aborted retest. Specifically, a different laboratory may need to perform a third test if one of the repeat tests performed at the original laboratory is non-reactive and the other is invalid. In addition, if the software bug will not allow the original laboratory to perform the repeat tests, they may be performed in a different laboratory that is using testing equipment and reagents from the same manufacturer of the tests in the original laboratory. If the initial test is reactive and one other test is reactive on the same specimen, a third screening test is not required.
- i. Distribute Whole Blood and associated components that were collected in a manner that was not consistent with the manufacturer's directions for the collection bag. Specifically, the tubing was not sealed in the proper order, but the system remained closed during this procedure and the safety, purity, or potency of the blood components was not affected.

- j. Deviate from the manufacturer's instructions for the Gen-Probe Procleix HIV-1/HCV Assay for specific tests runs that were performed in an area where the ambient temperature was 19 °C - 20 °C instead of 21 °C - 27 °C, as required in the manufacturer's instructions.
- k. Distribute 27 Rh negative Red Blood Cell units labeled as leukocyte reduced that were stored at 1-6 °C and filtered at day 4 after collection instead of day 3, as required by the filter manufacturer's instructions, provided all the units were tested and found to have white cell counts less than  $5 \times 10^6$ .
- l. Use FTA-ABS methodology as an alternative procedure to quantitative RPR testing on samples with a qualitative reactive RPR test for syphilis.
- m. To allow distribution of blood components collected from donors whose temperatures were determined in a manner that was not consistent with the package insert for the TempaDot Single Use Clinical Thermometer.
- n. Distribute 28 rare deglycerolized Red Blood Cell units that were not frozen within six days of collection as prescribed in the manufacturer's instructions.
- l. To distribute blood components prepared from 116 donors whose hemoglobin was determined using expired HemoCue microcuvettes. This approval was granted for the following reasons: (1) the Hb 301 controls run on the expired microcuvettes were within acceptable ranges and compared well to the controls run on the in-date microcuvettes; (2) the hemoglobin result for all the donors was  $\geq 12.6$  g/dL and (3) the problem analysis and corrective and preventative actions for this incident were adequate.
- m. To distribute Source Plasma collected from donors whose total protein was determined on a refractometer that was quality controlled on two days using expired reagents. The approval was granted for the following reasons: (1) the daily quality control performed on the instrument with expired reagents had acceptable results; (2) the quality control results from the day before and the day after the incident when in-date reagents were used revealed the instrument was operating consistently; (3) there were no repair reports in the past 11 months for the instrument; and (4) the preventative and corrective actions taken appear to be sufficient to prevent a similar occurrence.
- n. To allow distribution of 37 Apheresis Fresh Frozen Plasma units that were collected using expired needle sets because bacteria cultures taken from a sampling of the plasma units collected during the same time showed no growth 14 days after incubation and there is no direct evidence that the units were contaminated.
- o. Deviate from manufacturer's instructions and test in duplicate using the ABBOTT PRISM HBsAg assay, donor specimens that were initially reactive using the Genetic Systems HBsAg EIA 3.0 on the Ortho Summit platform. If either or both of the donor specimens test reactive using the ABBOTT PRISM HBsAg assay, the confirmatory testing must be performed using the ABBOTT PRISM HBsAg Confirmatory assay. The approval is in effect until the manufacturer of the Genetic Systems HBsAg EIA 3.0 assay resolves issues related to an increased incidence of initial reactive results when using the Genetic Systems HBsAg EIA 3.0 on the Ortho Summit platform.
- p. To allow the use of the following blood bank reagents that were stored at temperatures between 8 °C and 17 °C for about 15 hours: blood grouping, red blood cells, anti-human globulin and enhancement solutions. Approval was granted under the following conditions: (1) the reagents will be visually inspected before use and (2) the appropriate controls will be performed according to the manufacturer's instructions before use.
- q. To test samples from Red Blood Cell components collected and filtered in the Haemonetics in-line Whole Blood collection filter kit (Leukotrap RC System with RC2D Filter) for residual White Blood Cells (rWBC) beyond the 48-hour post filtration time found in the manufacturer's instructions for the rWBC counting kit using the flow cytometry device. This approval is specific for the Haemonetics Leukotrip RC System with RC2D Filter lot numbers distributed since April 14, 2016 involved in the filter recall.

- r. To manufacture Pooled Platelets – 5 Day using the Terumo BCT ELP accessory platelet storage bag or the Amicus X6R235/PL2410 platelet storage bag instead of the recalled Haemonetics Acrodose PLus System CLX-HP extended storage bag under specific conditions. This approval will expire when adequate supplies of Haemonetics Acrodose pooling sets are available.
- s. To perform bacterial testing using the BioMerieux BacT/Alert BPA system on pooled non-leukocyte reduced Whole Blood-derived platelets in the Acrodose PLus System.
- t. To distribute 68 platelet products that were tested using expired control reagents to determine residual white blood cell counts because the quality control results from the day before and the day after using in-date control reagents indicated the instrument was operating consistently.
- u. To distribute 22 Whole Blood units for which the samples used for Zika and WNV testing were collected in expired PPT tubes.
- v. To distribute 23 psoralen-treated apheresis platelets, leukocyte reduced, that were manufactured using expired Cerus INTERCEPT System processing kits.
- w. To repeat testing of donations initially reactive for anti-HBc on the Ortho VIP assay using the ABBOTT PRISM platform.
- x. To use the Alinity s Anti-HBc assay on the ABBOTT Alinity s platform for repeat testing of donor samples initially reactive for Ortho HBc ELISA Test System on the Verseia Integrated Pipetter (VIP) platform.
- y. To allow the temporary use of unfiltered pipette tips for post-PCR testing on the Immucor Precise Type HEA Molecular BeadChip Assay. The exception is permitted because filtered pipette tips were unavailable and is allowed only for the duration of the shortage.
- z. To leukocyte-reduce Red Blood Cells at 1° to 6 °C at a height of 142 cm instead of 165 cm as recommended by the manufacturer.
- aa. To leukocyte-reduce Red Blood Cells at 1° to 6 °C at a height of 135 cm instead of 165 cm as recommended by the manufacturer.
- bb. One-time exception to distribute Red Blood Cells, Leukocytes Reduced, Fresh Frozen Plasma and Recovered Frozen Plasma units, that were manufactured from donors whose hemoglobin was determined using expired HemoCue Hb 301 microcuvettes.

**6. 21 CFR 606.65(e) & 21 CFR 610.53(b)**

- a. To store apheresis platelets at refrigerator temperature (1-6 °C) without agitation for up to 3 days. The cold stored platelets will only be used in the resuscitation of actively bleeding patients. The new storage conditions will be reflected in Circular of Information.
- b. To manufacture Apheresis Platelets, Platelet Additive Solution (PAS-C) Added, Leukocytes Reduced, stored at 1-6 °C for up to 14 days without agitation. The cold stored platelets products are intended to treat actively bleeding patients through day 14 of storage when conventional platelet products are unavailable, or their use is not practical.
- c. To manufacture Apheresis Platelets, Leukocytes Reduced, Psoralen-Treated, stored at 1-6 °C for up to 14 days without agitation. The cold stored platelets products are intended to treat actively bleeding patients through day 14 of storage when conventional platelet products are unavailable, or their use is not practical.
- d. To manufacture Apheresis Platelets, Leukocytes Reduced, suspended in 100% plasma, stored at 1-6 °C for up to 14 days without agitation. The cold stored platelets products are intended to treat actively bleeding patients through day 14 of storage when conventional platelet products are unavailable, or their use is not practical.
- e. To manufacture Apheresis Platelets, PAS-F Added, Leukocytes Reduced, stored at 1-6 °C for up to 14 days without agitation. The cold stored platelets products will be used to treat actively bleeding patients through day 14 of storage when conventional platelet products are unavailable, or their use is not practical.

**7. 21 CFR 606.100(b):**

- a. Allow hearing-impaired donors to read the donor history questionnaire rather than the verbal presentation of the questions by center personnel as required in the firm's SOP, provided the high-risk behavior questions are still asked verbally or by an interpreter and unacceptable responses or responses that require follow-up questioning are asked by the interpreter. This approval is only for the blood drive involving hearing-impaired donors on a specific date.
- b. Allow a specific donor who had taken Proscar within the past 30 days to donate Source Plasma for further manufacturing into in vitro diagnostic reagents provided the medical director approves the donor's participation and the consignee accepts units from this donor. This approval is only in effect while the donor's specialized property is at sufficient levels for further manufacturing.
- c. To allow distribution of Red Blood Cells that took about 45 hours to ship but there are no records of the capacity of the shipping containers to maintain proper temperature in transit for more than 24 hours. The temperature of the Red Blood Cells upon arrival was 3.8 °C.

**8. 21 CFR 606.121:**

- a. Use of full-face green labels for autologous use only units.
- b. Use of "Autologous" on label in lieu of "Paid" or "Volunteer."
- c. Omit special labeling from Red Blood Cells 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.
- d. Place ABO/Rh label and "Donor Untested" on group and type label position.
- e. To not identify the antibody for autologous units that have a positive test for unexpected antibodies or include the antibody identity on the label or tie-tag for these autologous units, provided the tie-tag contains a statement that an irregular antibody is present and the autologous unit will not be used for allogeneic transfusions.

**9. 21 CFR 606.121(c)(3), 640.64(d) & 640.69(d):**

To relabel 79 Source Plasma units and test samples with new bleed numbers and distribute the units for further manufacture into non-injectable products. The units were inadvertently labeled with previously used bleed numbers. The new bleed numbers can be traced to the donor.

**10. 21 CFR 606.122:**

Extend the time to administration of a washed, irradiated platelet donated by the intended recipient's mother, to 5.5 hours because the time needed to process, test, prepare and transport the component would not allow administration to begin within the required 4-hour time period.

**11. 21 CFR 606.151:**

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

**12. 21 CFR 606.160**

- a. Allow distribution of Fresh Frozen Plasma for which there were no temperature records available for 3 days, provided there is no evidence to suggest that the safety, purity, or potency of the blood components were affected, and the documentation of the investigation of the incident and correction actions taken to prevent a similar

- incident from occurring, is available for review at the next FDA inspection.
- b. Allow distribution of blood components for which there were no temperature records available for approximately 12 hours, provided there is no evidence to suggest that the safety, purity, or potency of the blood components were affected, and the documentation of the investigation of the incident and correction actions taken to prevent a similar incident from occurring, is available for review at the next FDA inspection.
  - c. Allow distribution of two autologous units for which the blood donation records of the second donation were lost after the autologous donors were determined to be acceptable to donate. The donors' history and physical information is available in the records for the first donation.
  - d. Allow distribution of 43 units of Platelets, Pheresis, Leukocytes Reduced (representing 91% of available inventory) and 70 units of Platelet, Leukocytes Reduced (representing 100% of available inventory) for which there was no evidence of temperature monitoring for approximately 24 hours, provided: (1) there is a 100% visual inspection of the components and units with no evidence of swirling are discarded and (2) the Platelet, Leukocyte Reduced units have been pooled and tested for bacterial contamination before distribution.
  - e. Allow distribution of one autologous unit for which there were no storage temperature records available for approximately 8 hours, provided the unit was examined for hemolysis or unacceptable appearance.
  - f. Allow distribution of Red Blood Cells for which there are no recorded temperatures for about 44 hours because the chart was not properly attached to the recorder. This approval was granted because the refrigerator is continuously monitored by an external company and there were no alarms during the time the temperature was not recorded, and all the units will be inspected before distribution; units showing evidence of hemolysis or contamination will be destroyed.
  - g. Allow distribution of 34 Red Blood Cells, Leukocyte Reduced units for which there is no documentation of the sterile weld used to connect the leukocyte reduction filters, provided: (1) there is no evidence of a blood spill, (2) these units are distributed only if there are no other units available that were prepared according to SOPs, (3) the medical director will document the justification for releasing the units, (4) the units are visually inspected before distribution and this inspection is documented, and (5) the consignee is notified the sterile weld used to connect the leukocyte reduction filter was not documented.
  - h. To distribute Source Plasma units for which there are no temperature records due to a malfunction of the electronic temperature monitoring system. The approval was based on the data submitted to show there were no temperature excursions and the products were not impacted during the time the records were not available.

**13. 21 CFR 606.160(b):**

Allow distribution of blood and blood components collected from donors whose donation records were lost after they had donated, provided the medical history and examination had been completed, the donation records had been reviewed, and the donors and their records were determined to be acceptable prior to donation, and the donors were re-interviewed post-donation and records are maintained of this interview.

**14. 21 CFR 606.160(b) & 640.11(a):**

Allow distribution of Red Blood Cells for which there were no temperatures recorded for 5 hours, provided there was a 100% inspection of all units in the refrigerator at the time the temperatures were not recorded, and all unacceptable units were discarded.

**15. 21 CFR 610.40:**



- a. 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.
- b. Allow shipment under quarantine of untested Source Plasma labeled as tested negative, to warehouse operated by another manufacturer for storage until testing is completed.
- c. 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.
- d. Allow shipment under quarantine of Source Plasma that are labeled as negative/non-reactive for infectious diseases before completion of the infectious disease tests, to a contract off-site storage facility not operating under an U.S. license. Source Plasma manufacturer will cull and destroy reactive units according to their standard procedures.
- e. Allow shipment under quarantine of Source Plasma that is labeled as negative/non-reactive for infectious diseases before completion of the infectious disease tests, to a contract off-site storage facility for temporary storage during a forecasted hurricane, provided the cases are labeled "Untested" and "Biohazard." The Source Plasma will be returned to the center after the emergency for culling and distribution according to standard operating procedures.
- f. Allow shipment under quarantine of Source Plasma that is labeled as negative before completion of the HIV-1 RNA and HCV RNA nucleic acid tests, to a storage facility own by another licensed manufacturer for temporary storage during a freezer repair, provided the cases are labeled "Untested" and "Biohazard." The Source Plasma will be returned to the center after the repair for culling and distribution according to standard operating procedures.
- g. Distribute a single directed donor unit that was tested on a sample drawn 3 days after the directed donor unit was collected.
- h. Ship the first autologous donation within a 30-day period for which a sample was unavailable for testing, to another blood establishment that does not allow autologous units to be crossed over into allogeneic inventory, under the following conditions: (1) use the test results from a prior sample or donation collected within 30 days before the untested units, or use the test results from a subsequent sample or donation collected within 30 days after the untested unit and (2) label the untested units with the date the donor was tested; the statement: "All test results are negative or nonreactive within 30 days of donation date" or "Donor Untested," as appropriate; "For Autologous Use Only;" and "Biohazard," if applicable.

**16. 21 CFR 610.40(a) & 640.5(b)-(c):**

- a. Perform laboratory testing on two directed donor Red Blood Cell units using a specimen that was collected from the donor after the donation date, provided the units are not released until testing done on the new specimen has been completed.
- b. To discontinue testing of all donations with a licensed nucleic acid test for Zika virus, or discontinue using pathogen reduction technology, to reduce the risk of ZIKV transmission through the transfusion of blood and blood components.

**17. 21 CFR 610.46 & 610.47:**

To include language in the consignee notification that eliminates the need to notify transfusion recipients and perform testing and counseling for HIV-1 and HCV when the discriminatory NATs are non-reactive for both HIV-1 RNA and HCV RNA.

**18. 21 CFR 610.47(a)(3) & (b)(3):**

To use the results from a modified HCV testing algorithm in lieu of a supplemental test for purposes of notifying consignees of supplemental test results and determining whether notification of transfusion recipients of prior collections is required. In the absence of an approved HCV supplemental test, blood establishments may advise transfusion services that the donor was further tested under a modified testing algorithm. The notification of transfusion recipients is not required when the donor is repeatedly reactive on the anti-HCV screening assay but negative on a mini-pool or individual donation HCV NAT assay and non-reactive on a second anti-HCV screening assay.

**19. 21 CFR 610.50(a), 610.53 & 660.21(e):**

To allow the reagent manufacturer to define the dating period of blood grouping reagents (Anti-A, Anti-B, Anti-A,B, Anti-D and Anti-IgG) as 18 months from the date of filling.

**20. 21 CFR 610.53:**

- a. Extend CPD and CP2D liquid plasma expiration date to 42 days when stored at 1-6°C.
- b. Allow use of 53 vials of deglycerolized immunogen Red Blood Cells that were exposed to temperatures from 6 - 8 °C for up to 3 hours.
- c. Allow distribution of 2 units of autologous Red Blood Cells that were exposed to storage temperatures outside the acceptable limits provided: (1) the patient's physician is notified of the storage conditions and the possible risks; (2) the patient's physician had determined that it is medically necessary for the patient to receive these units; (3) the units are issued under the emergency release procedure; and (4) the blood bank medical director has approved the distribution of the units.
- d. Extend dating period of Platelets, Pheresis, Leukocytes Reduced, stored at 20 to 24°C, up to 7 days, provided: (1) the components are collected in the GAMBRO ELP storage containers; (2) with either the COBE Spectra or GAMBRO BCT Trima automated cell separator; (3) are release tested using the BacT/ALERT Microbial Detection System; and (4) the blood establishment participates in the GAMBRO BCT PASSPORT protocol and annually submits information to FDA for post-market surveillance.
- e. To allow use of Fresh Frozen Plasma (FFP) units that were exposed to storage temperatures warmer than -18 °C (specifically -9 °C) during Hurricane Katrina provided: (1) these units remained frozen; (2) the units were quarantined and only used in an emergency when no other FFP was available; (3) these units will be replaced as soon as possible; and (4) once the supply has been replaced, any remaining FFP that was exposed to temperatures warmer than -18 °C, will be destroyed.
- f. To allow distribution of Cryoprecipitated AHF, Cryoprecipitated AHF Pooled and Fresh Frozen Plasma that were stored at temperatures between -18 °C and -15 °C for no longer than one hour, provided all units were examined for evidence of thawing and found acceptable before distribution and the consignees were notified of the storage temperature deviation and quality assurance evaluation.
- g. One-time exception to allow the release of Red Blood Cells (used for immunizing Source Plasma donors) that were exposed to temperatures above -65 °C for a maximum time of 1.5 hours, provided certain conditions are met.

**21. 21 CFR 610.53(b) & 640.11(a)**

One-time exception to allow the distribution of frozen Red Blood Cell units with rare antigens that were exposed to temperatures warmer than -65 °C for a maximum time of 11 hours, with the warmest temperature reaching -66.96 °C, provided certain conditions are met.

**22. 21 CFR 610.53(b) & 640.34(b)**

- a. One-time exception to allow the distribution of Fresh Frozen Plasma units that were exposed to temperatures warmer than -18 °C for approximately 4 hours, with the warmest temperature reaching -14.4 °C, provided certain conditions are met.
- b. One-time exception to distribute frozen blood products (Fresh Frozen Plasma, Pooled Cryoprecipitated AHF) that were exposed to temperatures warmer than -18 °C for approximately 9.5 hours with the warmest temperature reaching -15 °C, provided certain conditions are met.

**23. 21 CFR 630.10(a), 630.10(e), 630.10(h), 630.30(b)**

To collect and distribute Whole Blood from otherwise-eligible donors who would have been deferred for vCJD risk due to time spent in countries or on military bases, other than the UK, France and Ireland, use of prescription Finasteride in past month or Dutasteride in past 6 months, or travel to a malaria-endemic area in the past one year prior to the donation attempt. The Whole Blood collected from these donors will only be further manufactured into non-injectable reagent red blood cells.

Note: FDA no longer recommends deferral for vCJD geographic risk. Also, FDA currently recommends a three-month deferral for travel to a malaria by residents of non-endemic countries.

**24. 21 CFR 630.10(e)(2)(ii) & 606.100(b)(1)**

To distribute blood components prepared from 70 allogeneic donors who received the Adenovirus, MMR and Varicella vaccines and donated within the 28-day deferral period specified in the SOP.

**25. 21 CFR 630.15(b)(1)(iii)**

One-time exception to distribute a rare Source Plasma unit collected from a donor with systemic lupus erythematosus (SLE) for which a new medical history and physical examination was not conducted.

**26. 21 CFR 630.30(a)(2) & 630.30(b)(1)**

- a. To distribute seven Apheresis Red Blood Cell units, that when collected, resulted in the donor exceeding their annual accumulated blood loss.
- b. To distribute 185 Source Plasma units collected from 150 donors who did not have the SPE/STS sample collected on the first donation or physical examination, as required in 21 CFR 640.65(b)(1)(i).

**27. 21 CFR 630.30(b)(1) & 630.15(b)(6)(iii)**

One-time exception to release units of Source Plasma collected from donors who had exceeded the Red Blood Cell loss limit and should have been deferred under 21 CFR 630.15(b)(6)(iii).

**28. 21 CFR 630.30(b)(1) & 640.65(b)(1)(i)**

- a. One-time exception to distribute Source Plasma units collected from donors who did not have a serum protein electrophoresis (SPE) and serological test for syphilis (STS) sample collected for testing on the day of their initial physical exam or plasmapheresis, provided that the implicated Source Plasma units are released as follows:

- (1) Units collected from donors who had a follow-up SPE/STS test with acceptable results may be released for further manufacture into injectable products; and
- (2) Units collected from donors who did not have a follow-up SPE/STS test may only be released for further manufacture into non-injectable products.
- b. One-time exception during a public health emergency to distribute Source Plasma units collected from donors who did not have a serum protein electrophoresis (SPE) and serological test for syphilis (STS) sample collected for testing on the day of their initial physical exam or plasmapheresis provided that:
  - (1) The units collected from donors who did not have a follow-up SPE/STS sample collected will be used for further manufacturing into noninjectable products only; and
  - (2) The units collected from donors who had a follow-up SPE/STS sample collected and tested and the results were acceptable may be used for further manufacturing into injectable products.
- c. One-time exception during weather-related disaster conditions and a public health emergency to distribute Source Plasma units for further manufacture which were not tested for serum protein electrophoresis (SPE) on the first donation provided all other required testing has been performed and an SPE sample is obtained on the donor's next donation.
- d. One-time exception to distribute for further manufacture into non-injectable products, a rare Source Plasma unit collected from a donor with factor XIII deficiency, for which the serum protein electrophoresis (SPE) and serological test for syphilis (STS) were not performed.

**29. 21 CFR 640.3 (current 21 CFR 630.10 & 630.15):**

- a. To allow individuals with hereditary hemochromatosis with hematocrits of 34% or greater or hemoglobins of 11.5 g/dL or greater, to donate 500 mL of Whole Blood, provided that only Red Blood Cells are prepared from the Whole Blood donation. In addition, the Red Blood Cells must contain special labeling to show that its contents are equal to or greater than the contents of a standard 450 mL collection bag. These Red Blood Cells may be used for allogeneic transfusions.
- b. Allow distribution of blood and blood components collected from donors who may not have been provided the written educational materials and AIDS information, as required by written SOPs, from June 2004 to November 2004, provided (1) the donors otherwise meet the requirements for allogeneic blood donation; (2) the results of all infectious disease testing are negative; (3) repeat donors had donated successfully on at least one previous occasion at a facility operating under the same license number; and (4) the infectious disease test results on an additional sample collected within 2 weeks from first-time donors are negative and these donors were contacted and provided information about the signs and symptoms of AIDS.
- c. To allow distribution of Platelets Pheresis products from a donor who temperature was performed immediately after donation, instead of prior to collection, provided the temperature taken immediately after donation was acceptable and all listed corrective actions to prevent a recurrence have been implemented.
- d. To determine the eligibility of a group of donors by contacting them more than 24 hours after their donations to verify the health history information obtained on three questions that were incorrectly translated into Spanish with the provision that products collected from donors who cannot be contacted will be discarded.

**30. 21 CFR 640.4(h) & 640.11(a):**

- a. Allow use of Whole Blood and Red Blood Cells 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.
- b. Allow distribution of autologous Whole Blood and Red Blood Cell units that were

stored at temperatures outside the acceptable limits for 6 hours, provided: (1) the patient's physician was notified of the storage conditions and the possible risks to the safety, purity and potency of the components; (2) the patient's physician has approved that the components are medically necessary for the patient; (3) the units were released by the emergency release procedure; and (4) the blood bank medical director has approved the release of the units.

**31. 21 CFR 640.5:**

- a. Allow specimens used for NAT assay to be collected up to 24 hours prior to the collection of heparinized Whole Blood units.
- b. Allow distribution of 1,398 units collected from repeat donors using the historical check as the second ABO group instead of performing a second ABO group on a sample taken from the donor during donation, provided the results of the serological ABO test and historical check agree.

**32. 21 CFR 640.11(a):**

- a. Allow use of Red Blood Cells and Red Blood Cell 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.
- b. Allow use of Red Blood Cells that were exposed to temperatures between 6 °C to 10.5 °C for up to 4.75 hours, provided each unit was examined for hemolysis before distribution.
- c. Allow distribution of Red Blood Cells that were exposed to storage temperatures warmer than 6 °C, but no warmer than 10 °C for less than 4 hours, provided the units were examined and there was no evidence of hemolysis or contamination.
- d. Allow distribution of Red Blood Cells that were exposed to storage temperatures warmer than 6 °C, but no warmer than 7.85 °C on 2 occasions for a total of 2.75 hours, provided the units were examined and there was no evidence of hemolysis or contamination.
- e. Allow distribution of Red Blood Cells that were exposed to storage temperatures warmer than 6 °C, but no warmer than 11.9 °C for a total of 40 minutes, provided the units were examined and there was no evidence of hemolysis.
- f. Allow distribution of Red Blood Cells that were exposed to storage temperatures warmer than 6 °C, but no warmer than 11.8 °C for a total of 3 hours, provided the units were examined and there was no evidence of hemolysis.
- g. Allow distribution of Red Blood Cells and Red Blood Cells, Leukocytes Reduced that were exposed to storage temperatures warmer than 6 °C, but no warmer than 8°C, for a total of 1 hour and 15 minutes, provided the units were examined and there was no evidence of hemolysis or contamination.
- h. Allow distribution of Red Blood Cells that were exposed to storage temperatures between 6 °C and 8 °C for approximately 30 minutes, provided the units were examined and there was no unacceptable appearance or evidence of hemolysis.
- i. Allow distribution of Red Blood Cells, Leukocytes Reduced that were exposed to storage temperature of 6.5 °C for no more than 16 hours, provided the units were examined and there was no evidence of hemolysis.
- j. Allow distribution of Red Blood Cells, Leukocytes Reduced, representing the entire inventory of red blood cell units, which were exposed to storage temperatures warmer than 6 °C, but no warmer than 8.21 °C for approximately 2 hours and 55 minutes, provided the units were examined for evidence of hemolysis or contamination before distribution.
- k. Allow distribution of 1,001 Red Blood Cells representing the entire inventory of red blood cell units, which were exposed to storage temperatures colder than 1°C but no colder than 0.71 C for approximately 15 minutes, provided the units were examined for evidence of hemolysis or contamination before distribution and the consignees

were notified of the storage temperature deviation and quality assurance evaluation.

- I. One-time exception to allow the release of Red Blood Cells (used for immunizing Source Plasma donors) that were exposed to temperatures between 6.0°C and 6.8°C for approximately 20 minutes, provided certain conditions are met.

**33. 21 CFR 640.16(a):**

Allow distribution of 2 autologous Red Blood Cell units that were not prepared within the timeframe specified in the directions for use for the blood collecting, processing and storage system, provided: (1) the units are tested for bacteria contamination, (2) the patient's physician is notified of the incident, (3) the units are quarantined and examined for hemolysis until issued for transfusion, and (4) the units are issued as an emergency release.

**34. 21 CFR 640.17 & 610.53(c) (current 21 CFR 610.53 (b)):**

- a. To allow distribution of rare antigen negative deglycerolized Red Blood Cells that were previously stored frozen at temperatures warmer than -65 °C for a short time provided the frozen units are visually inspected for hemolysis before deglycerolizing and the following tests are performed on the deglycerolized RBCs: RBC recovery, free hemoglobin and residual glycerol testing.
- b. Distribute rare deglycerolized Red Blood Cell units that were stored frozen between -57.9 °C to -65 °C for approximately 3 hours provided all frozen units will be examined for evidence of thawing and hemolysis before deglycerolization, all consignees will be notified of the storage temperature deviation, and the records of the incident will be available for review during FDA inspections.
- c. To distribute for injection aliquots of deglycerolized immunogen Red Blood Cells that were previously stored frozen at temperatures warmer than -65 °C for a short time provided the center medical director has reviewed the documentation of the incident and has approved the release of the cells for red blood cell immunization.
- d. To distribute 171 units of Frozen Red Blood Cells that were stored at temperatures between -63.8 °C and -65 °C for about 42 minutes. The units were inspected for signs of damage, gross contamination, thawing and hemolysis before deglycerolization and quality controlled for RBC recovery, free hemoglobin and hematocrit before final distribution.

**35. 21 CFR 640.23(b):**

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

**36. 21 CFR 640.24(a) & 21 CFR 606.65(e)**

Time-limited approval to manufacture Acrodose Pooled Platelets, pooling as early as 12 hours instead of 24 hours as described in the Instructions for Use

**37. 21 CFR 640.25(a):**

- a. Allow distribution of two Platelets, Pheresis units that were stored at temperatures between 23.4 °C and 24.2 °C for approximately 4½ hours provided the units are examined for evidence of contamination prior to distribution and the medical director approves the release of the units.
- b. One-time exception to allow the release of Apheresis Platelets units for which continuous gentle agitation was not maintained for up to 2 hours during storage, provided certain conditions are met.

**38. 21 CFR 640.25(a) & 606.65(e):**

Allow distribution of plateletpheresis components that were not continuously gently agitated during storage for 7 - 12 hours.

**39. 21 CFR 640.25(b):**

- a. Discontinue the determination of the platelet count and plasma volume (and calculation of platelet yield) of Platelets Pheresis products at the end of the storage period (at issue or outdate), provided the target platelet yield guarantees individual transfusable components have an adequate platelet yield after removal of bacterial and quality control testing samples and pH testing continues to be performed at issue or outdate.
- b. Use of the pre-sample plasma volume, instead of the post-sample actual product plasma volume, for the determination of the platelet count for quality control testing performed at the end of the storage period, provided the residual WBC count, pH and platelet yield are performed on the same Platelets, Leukocytes Reduced selected for testing.

**40. 21 CFR 640.32(b):**

Relabel Fresh Frozen Plasma collected by apheresis as Recovered Plasma prior to expiration of the original product. (Done to manage Fresh Frozen Plasma inventory collected during periods of increased risk for West Nile Virus.)

**41. 21 CFR 640.34:**

- a. Allow use of A and AB Fresh Frozen Plasma 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.
- b. Allow use of 45 units of Fresh Frozen Plasma 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.
- c. Allow distribution of 1,201 units of Fresh Frozen Plasma 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.

**42. 21 CFR 640.34 & 640.54(a):**

- a. Allow distribution of 1,235 units of Fresh Frozen Plasma 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.
- b. Allow distribution of Fresh Frozen Plasma, Plasma frozen within 24 hours, Plasma Cryoprecipitate Reduced, Cryoprecipitated AHF and Cryoprecipitate rich plasma that were exposed to storage temperatures between -10.1 °C and -18 °C during 2 excursions over 2 days for a total of 3 hours 18 minutes, provided the safety, purity, or potency of the components was not affected.
- c. Allow distribution of one autologous Cryoprecipitated AHF unit for which the plasma was not placed in the freezer until 11 hours after collection. This was approved because the product was collected to be used for its fibrinogen content and not for its Factor VIII content.

**43. 21 CFR 640.54(a)(2) & 606.65(e)**

- a. To manufacture Cryoprecipitated AHF and Pooled Cryoprecipitated AHF from Plasma Frozen Within 24 Hours After Phlebotomy (PF24).
- b. To manufacture Plasma, Cryoprecipitate Reduced from Plasma Frozen Within 24 Hours After Phlebotomy (PF24).

**44. 21 CFR 640.56(b)**

To allow specific blood establishments to receive the Cryoprecipitated AHF quality control results more than 30 days, but no later than 45 days, from the date of preparation of the product.

**45. 21 CFR 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.

**46. 21 CFR 640.69(e)&(f):**

To distribute Source Plasma collected from paid COVID-19 convalescent donors at their first donation (21 CFR 640.69 (e)) and without a quarantine hold (21 CFR 640.69 (f)) by blood establishments licensed to collect Source Plasma, intended for further manufacture into licensed COVID-19 Hyperimmune Globulin (Anti-COVID-19 H-IG).

**47. 21 CFR 640.76:**

- a. 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.
- b. 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.
- c. Allow 600 L. 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."
- d. 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.
- e. Allow Source Plasma that was inadvertently exposed to a storage temperature warmer than -20 °C and colder than -14 °C for 2.5 hours to not be relabeled as "Source Plasma, Salvaged," provided the plasma was not allowed to thaw.
- f. To issue, without relabeling as 'Source Plasma Salvaged,' Source Plasma units intended for further manufacturing into injectable products after being exposed to a storage temperature warmer than -20 °C and colder than +10 °C for 2 hours and 57 minutes provided the plasma did not show signs of thawing.
- g. One-time exception to allow Source Plasma units intended for further manufacturing into injectable products, which were exposed to more than one episode of storage temperature fluctuations warmer than -20 °C and colder than -5 °C for approximately 1.5 hours, to not be relabeled as "Source Plasma Salvaged" provided that the plasma remained frozen solid and the consignee is notified of the temperature deviations.
- h. One-time exception to allow the issuance of Source Plasma units intended for further manufacturing into injectable products that were exposed to more than one episode of temperature fluctuations warmer than -20 °C and colder than -5 °C for approximately 40 hours and 52 minutes without relabeling as Source Plasma Salvaged, provided the plasma remained frozen solid and the consignee is notified of the temperature deviations.



- i. One-time exception to allow Source Plasma units intended for further manufacturing into injectable products to not be relabeled as Source Plasma Salvaged. The units were exposed to more than one episode of temperature fluctuations warmer than -20 °C and colder than +10 °C for approximately 19 hours and 55 minutes and remained frozen solid. In addition, the consignee will be notified of the temperature deviation.
- j. One-time exception to allow Source Plasma units intended for further manufacturing into injectable products to not be relabeled as "Source Plasma Salvaged". The units were exposed to shipping temperature fluctuations warmer than -5 °C and colder than +10 °C for approximately 14 hours and 30 minutes and remained frozen solid. In addition, the consignee will be notified of the temperature deviation.
- k. One-time exception to allow Source Plasma units intended for further manufacturing into injectable products to not be relabeled as "Source Plasma Salvaged". The units were exposed to more than one episode of storage temperature fluctuations warmer than -20 °C and colder than +10 °C for approximately 5 hours and remained frozen solid. In addition, the consignee will be notified of the temperature deviation.
- l. One-time exception to allow Source Plasma units intended for further manufacturing into injectable products to not be relabeled as "Source Plasma Salvaged". The units were exposed to storage temperature fluctuations warmer than -20 °C and colder than +10 °C for approximately 2 hours and 30 minutes and remained frozen solid. In addition, the consignee will be notified of the temperature deviation.