Exceptions and Alternative Procedures Approved Under 21 CFR 640.120

Title 21 Code of Federal Regulations 640.120(a) - The Director, Center for Biologics Evaluation and Research, may approve an exception or alternative procedures to any requirement in subchapter F (Biologics) of Chapter I (Parts 600 - 680) 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 procedure to the requirements in Parts 600-680. Licensed establishments should submit the request in accordance with 21 CFR 601.12 and may reference our guidance document entitled: Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture (July 2001).

Requests for such exceptions or alternative procedures should ordinarily be made in writing, however, in limited circumstances, such requests may be made orally and permission may be given orally by the Director. Oral requests and approvals must be promptly followed by written requests and written approvals.

It should be noted that requests for exceptions or alternate procedures includes specific circumstances and may require submission of supporting data unique to the circumstance. Publication of these approvals for a specific exception or alternative procedure does not necessarily mean that they can be generally applied to other manufacturers.

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21 CFR 640.120 APPROVALS

As of May 28, 2018, the following exceptions or alternative procedures have been approved under 21 CFR 640.120. The exceptions or alternative procedures that were approved in May 2018 are identified with an asterisk (*).

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.

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 digital thermometer according to the schedule recommended by manufacturer, instead of monthly as required by regulation. [Variance request no longer needed when following manufacturer's instructions, as required by 21 CFR 606.65(e)]

b. 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.

c. 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.

d. 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.

e. 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.

f. 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.

g. 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.

4. **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 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).
    e. 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.
    f. 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.
    g. 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.
    h. 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 5x10e6.
    i. Use FTA-ABS methodology as an alternative procedure to quantitative RPR testing on samples with a qualitative reactive RPR test for syphilis.
    j. 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.
    k. 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

≥ 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 distribute Whole Blood-derived platelets for neonatal and pediatric use that were tested using a rapid bacterial detection test for which the package insert does not include individual Whole Blood-derived platelets in its intended use. [Variance request no longer needed when following manufacturer's instructions, as required by 21 CFR 606.65(e)]

r. 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.

s. To perform rapid bacterial detection testing on single units of Whole Blood-derived platelets intended for neonatal and pediatric patients using the Verex Biomedical Incorporated Platelet PGD test.

t. * To manufacture Pooled Platelets – 5 Day using the Terumo BCT ELP accessory platelet storage bag in place of the Haemonetics Acrodose pooling set under specific conditions. This approval will expire when adequate supplies of Haemonetics Acrodose pooling sets are available.

5. 21 CFR 606.65(e) & 610.53(c)

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.

6. 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.

7. **21 CFR 606.121:**

a. Use of full face green labels for autologous use only units.
b. Use of black print for all statements on container labels (omit use of statements in red print). [Regulation revised - variance request no longer needed]
c. Use of "Autologous" on label in lieu of "Paid" or "Volunteer."
d. 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.
e. Place ABO/Rh label and "Donor Untested" on group and type label position.
f. Print the anticoagulant name after the proper product name instead of preceding it. (Done for ISBT 128 labels.)
g. 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 used for allogeneic transfusions.

8. **21 CFR 606.122:**

a. Extend the storage time of thawed Fresh Frozen Plasma at 1-6°C to 24 hours, instead of 6 hours. [Regulation revised - variance request no longer needed]
b. 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.

9. **21 CFR 606.151:**
    a. Omit performing a minor side crossmatch on red blood cells prepared in additive solutions that have not been screened for unexpected antibodies.
    b. Use of a computer (electronic) crossmatch instead of a major side crossmatch. [Regulation revised - variance request no longer needed]
    c. Use of a type and screen procedure as an alternative method for the antiglobulin crossmatch. [Regulation revised - variance request no longer needed]
    d. Allow use of a recipient sample up to 72 hours old for pre-transfusion testing. [Regulation revised - variance request no longer needed]

10. 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, 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, 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.

11. 21 CFR 606.160(b) & 640.3(a):

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.

12. 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.

13. 21 CFR 607.35(a):

To send all validated copies of Form FD-2830 (Blood Establishment Registration and Product Listing) only to the reporting official for the establishment instead of each location shown on the registration forms.

14. **21 CFR 610.40:**

a. 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]
b. Ship autologous blood unit to another establishment without testing unit for communicable disease agents. Testing will be performed on either a sample or subsequent donation that is collected within 30 days of the original donation.
c. 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.
d. Allow shipment under quarantine of untested Source Plasma labeled as tested negative, to warehouse operated by another manufacturer for storage until testing is completed.
e. Reinstate one donor with non-discriminated NDR results 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.
f. 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.
g. 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.

h. Ship autologous blood unit to another establishment without testing unit for communicable disease agents under the following conditions: (1) neither facility has a crossover policy; (2) both establishments belong to the same university hospital system; (3) both establishments have the same medical director; and (4) both establishments share the same computer system.
i. 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.
j. Ship autologous blood unit to another establishment without testing unit for communicable disease agents under the following conditions: (1) the medical director and surgeon were informed that the units were not tested; and (2) the units were appropriated labeled as required by the Code of Federal Regulations.
k. 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.
l. Use a licensed individual donation HIV-1 NAT to replace the HIV-1 p24 antigen neutralization test to re-enter donors who were previously HIV-1 p24 antigen positive. A licensed individual donation HIV-1 NAT may be used to re-enter donors with a repeatedly reactive HIV-1 p24 antigen test and either an indeterminate or positive HIV-1 p24 neutralization test, provided that the individual donation HIV-1 NAT and anti-HIV antibody EIA screening test are performed on a follow-up sample collected 8 weeks after the indeterminate or positive HIV- p24 neutralization test result. If the individual donation HIV-1 NAT and anti-HIV antibody EIA screening tests are negative, the donor may be re-entered and donate. The donation must be tested as required in 21 CFR 610.40(a).
m. Discontinue HCV NAT on Source Plasma collected from Hemophilia A or Hemophilia B donors who are known to be reactive for HCV antibody, provided that the units are properly labeled and will only be used for further manufacture into non-injectable products.
n. Distribute a single directed donor unit that was tested on a sample drawn 3 days after the directed donor unit was collected.
o. Discontinue HCV NAT and Anti-HCV testing on Source Plasma collected from hemophiliac donors who are known to be reactive for HCV NAT and/or HCV antibody, provided that the units are properly labeled and will only be used for further manufacture into non-injectable products.
p. 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.

15. 21 CFR 610.40(e) & 630.6(a):

a. Discontinue supplemental testing for HCV for each donation with a repeatedly reactive anti-HCV EIA screening test only if the individual donation HCV NAT is reactive or discriminatory reactive using HCV primers. The supplemental testing for HCV must still be performed on all donations with a repeatedly reactive anti-HCV EIA screening test and a HCV NAT that is non-reactive or discriminatory non-reactive. Also exempt from obtaining HCV supplemental test results prior to donor notification for these donors. Donors must still be notified of their deferral and the reason for the deferral, including the HCV NAT results.

b. Discontinue supplemental testing for HBV for each donation with a repeatedly reactive HBsAg screening test only if the individual donation HBV NAT is reactive. The supplemental testing for HBV must still be performed on all donations with a repeatedly reactive HBsAg screening test and a HBV NAT that is non-reactive. Also exempt from obtaining HBV supplemental test results prior to donor notification for these donors. Donors must still be notified of their deferral and the reason for the deferral, including the HBV NAT results.

16. **21 CFR 610.40(e), 610.46(b) & 630.6(a):**

a. Discontinue supplemental testing for HIV-1 and HCV for each donation with a repeatedly reactive anti-HIV and anti-HCV EIA screening test only if the individual donation HIV-1 and HCV NAT is reactive or discriminatory reactive using HIV-1 and HCV primers. The supplemental testing for HIV-1 and HCV must still be performed on all donations with a repeatedly reactive anti-HIV and anti-HCV EIA screening test and a HIV-1 and HCV NAT that is non-reactive or discriminatory non-reactive. Also exempt from obtaining HIV-1 and HCV supplemental test results prior to donor notification for these donors. Donors must still be notified of their deferral and the reason for the deferral, including the HIV-1 and HCV NAT results. In addition, exempt from notifying consignees of the results of the HIV-1 supplemental testing. Consignees must still be notified of the results of the repeatedly reactive anti-HIV EIA screening test and reactive or discriminatory reactive HIV-1 NAT results within 30 calendar days after the repeatedly reactive anti-HIV EIA results.

b. Discontinue supplemental testing for HIV-1 for each donation with a repeatedly reactive anti-HIV EIA screening test only if the individual donation HIV-1 NAT is reactive or discriminatory reactive using HIV-1 primers. The supplemental testing for HIV-1 must still be performed on all donations with a repeatedly reactive anti-HIV EIA screening test and a HIV-1 NAT that is non-reactive or discriminatory non-reactive. Also exempt from obtaining HIV-1 supplemental test results prior to donor notification for these donors. Donors must still be notified of their deferral and the reason for the deferral, including the HIV-1 NAT results. In addition, exempt from notifying consignees of the results of the HIV-1 supplemental testing. Consignees must still be notified of the results of the repeatedly reactive anti-HIV EIA screening test and reactive or discriminatory reactive HIV-1 NAT results within 30 calendar days after the repeatedly reactive anti-HIV EIA results.

17. 21 CFR 610.40(a) & 640.5(a – c):

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.

18. 21 CFR 610.40(e):

Discontinue supplemental testing for HIV and HCV on subsequent donations from donors who are confirmed positive for Anti-HIV and Anti-HCV. These donors participate in a Source Plasma High Risk Donor program and their plasma will be used for further manufacturing into noninjectable products.

19. 21 CFR 610.40(g)

To ship a Source Plasma unit collected from a donor known to be HAV NAT positive for which the infectious disease screening tests were completed, but the nucleic acid tests (NAT) were not completed before shipment to the consignee. The unit will be labeled according to 21 CFR 606.121(h) to reflect what testing was completed and not completed before shipment and include the statement "Caution: For Use in Manufacturing Noninjectable Products Only." The consignee will perform the NAT tests upon receipt instead of the applicant's contract test laboratory.

20. 21 CFR 610.46, 610.47 and 610.48:

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.

21. **21 CFR 610.47(a)(3) and (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.

22. **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.

23. **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^{o}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.

24. 21 CFR 630.10(c)(2):

To determine eligibility of donors by contacting them more than 24 hours after donation to obtain missing information related to travel in areas with active Zika transmission.

25. **21 630.10(e)(2)(iii)**:

To test certain at-risk blood donors in areas without active Zika transmission instead of deferring them. These donors may provide a history of residence or travel to an area with active Zika transmission or sexual contact in the past 4 weeks with a male who traveled or resided in an area with active Zika transmission within 3 months prior to the sexual contact. The donors will be tested using an individual donor sample NAT (ID-NAT) using an investigational donor screening ZIKV NAT under IND. This approval is no longer applicable if active Zika transmission is determined.

26. 21 CFR 630.10(f)(2):

*To use an alternate procedure for hemoglobin determination that will allow the continued use of the OrSense NBM-200 device for one year pending the regulatory submission and 510(k) clearance of the OrSense NBM-200 device for hemoglobin determination in blood donors.

27. **21 CFR 640.3:**

a. Allow whole blood collection from autologous donors who don't meet donor suitability requirements.
b. Allow Whole Blood collection from donors with a history of hepatitis before age 11. [Regulation revised - variance request no longer needed]
c. Allow 4 week intervals between Fresh Frozen Plasma donations when it is collected as a by-product of a plateletpheresis procedure.
d. Allow individuals with hereditary hemochromatosis to donate blood and blood components more frequently than every eight 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.
e. Allow post-donation requalification after day of donation of donors who used an outdated vCJD donor questionnaire.
f. To allow individuals with hereditary hemachromatosis 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.
g. To defer donors for 180 days who have been exposed to HAV as a result of the outbreak in the Chi-Chi's restaurant in Pittsburgh, PA, instead of 12 months as required in the regulation. [FDA approved a modification that would allow a 120-day deferral timeframe.]
h. 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.
i. Allow determination of donor eligibility after day of donation of a directed donor who failed to mark the "I am female" response, provided she was re-interviewed and provided appropriate responses and had negative infectious disease test results.
j. Allow an individual with a hemoglobin of 10.8 g/dL to donate one unit of Whole Blood so that the platelets from this units can be used to treat the donor's child.
k. To deviate from previously approved SOPs for determining donor eligibility to collect blood from donors who received licensed vaccines 27 days prior to donation, instead of 28 days as required by SOPs. This is a one-time exemption.
l. Allow distribution of specific Red Blood Cell units collected from donors who had donated approximately one week prior to the required 8 week donation interval, provided all donors met the other donor eligibility criteria in 21 CFR 640.3(b) and 640.3(c), including acceptable hemoglobin results, and the donors stated that they did not experience any adverse reactions as a result of the donation. This is a one-time exemption.
m. 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.
n. 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.

o. Allow individuals on prescription testosterone to donate blood and blood components more frequently than every eight weeks without examination or certification of health by physician at time of donation, provided the donor is referred with a prescription by a physician containing instructions regarding frequency of phlebotomy and hematocrit/hemoglobin limits and to be exempt from placing special labeling about the donor's disorder on the blood components. This approval is granted under the condition that only the Red Blood Cells collected from these individuals may be distributed; the plasma and platelet components from these individuals should not be distributed for transfusion.

28. **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.

29. **21 CFR 640.5:**
    a. Allow syphilis testing to be performed on 27 donors on a substitute sample drawn after day of donation.
    b. Allow specimens used for NAT assay to be collected up to 24 hours prior to the collection of heparinized Whole Blood units.
    c. 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.

30. **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.

31. 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.

32. **21 CFR 640.17 & 610.53(c)**:

a. To allow distribution of rare antigen negative deglycerolized Red Blood Cells that were previously stored frozen at temperatures warmer than -65C 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 -65C 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 -63.8C and -65C 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.

33. **21 CFR 640.23(b):**

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

34. 21 CFR 640.24(a)

Allow storage for up to 5 days of Platelets prepared from Whole Blood that are leukocyte reduced and pooled prior to storage, provided the platelets are pooled and stored in a set approved for this use and the pooled platelets are tested for bacterial contamination. [Regulation revised - variance request no longer needed if using a blood collecting, processing, and storage system approved for such use by FDA and are following the manufacturer's instructions]

35. **21 CFR 640.25(a)**

Allow distribution of two Platelelets, Pheresis units that were stored at temperatures between 23.4 and 24.2 C for approximately 4 ½ hours provided the units are examined for evidence of contamination prior to distribution and the medical director approves the release of the units.

36. **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.

37. 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.

38. **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.)

39. **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 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."
    c. 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.
    d. 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.

40. **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.

41. **21 CFR 640.61, 640.62, & 640.63:**
    a. Permit trained staff to explain the hazards of plasmapheresis and obtain informed consent.
    b. 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.

42. **21 CFR 640.63:**
    a. Draw one donor with a rare red blood cell antibody who was Anti-HCV positive.
    b. Draw a donor with IgM Anti-HAV with a disease state program approval.

c. Allow plasmapheresis of an asymptomatic donor with a history of Lyme Disease, provided product is labeled that it was collected from donor with history of Lyme Disease.
d. Allow a donor with a slightly abnormal Serum Protein Electrophoresis to donate for an Infant Botulism Program.
e. Allow individuals with childhood history of hepatitis at age 10 or younger to donate. [Regulation revised - variance request no longer needed]
f. Allow Source Plasma to be collected from a specific anti-e donor whose weight fluctuates between 108-112 lbs to donate, provided the weight does not drop below 108 at time of donation and donor meets all other eligibility requirements.
g. Allow collection and distribution of Source Plasma for further manufacturing into non-injectable products from a donor known to have Chagas Disease

43. 21 CFR 640.63 & 640.65:

Allow an infrequent plasmapheresis collection program (every 28 days or less frequently). Donors may donate without a physical examination or plasma or serum protein tests.

44. **21 CFR 640.65:**
a. Allow an infrequent plasmapheresis program in Source Plasma facilities. Donors may donate without a physical examination or Serum Protein Electrophoresis.
b. Allow collection of Source Plasma from anti-HCV reactive donors with elevated SPE results (no more than 25% over normal limits established by testing lab), provided the donor's personal physician has given written approval.

45. **21 CFR 640.31(b), 640.32(b), 640.63 and 640.65**:

To collect Fresh Frozen Plasma more frequently than every four weeks during the collection and preparation of Platelets Pheresis, Leukocytes Reduced, PAS C (Intersol).

46. **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.

47. 21 CFR 640.70(a)(10):

To distribute Source Plasma units without relabeling the units with the proper name of the manufacturer, provided (1) the license number was correct on the label; (2) the parent corporation is the same for both manufacturers; (3) the paperwork accompanying the shipment will bear the correct manufacturer's name; and (4) the manufacturer will place a "Notice of Plasma Label Discrepancy" in each carton containing units labeled with the incorrect manufacturer's name.

48. **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.

49. **21 CFR 660.22:**

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

50. **21 CFR 660.28:**

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