



WELCOME

Ask the FDA and CMS/CLIA

2022 AABB Virtual Annual Meeting

November 6-7

Faculty Disclosure

In compliance with ACCME policy, AABB requires the following disclosures to the session audience

The following Regulatory Affairs Staff have no financial disclosures:

Director, Regulatory Affairs:

- Karen Palmer MT(ASCP) CQA(ASQ)

Senior Manager, Volunteer Engagement

- Arnold McKinnon, BA

If you have questions following this session, please contact us:
regulatory@aabb.org

Objectives

- Evaluate existing practices to establish alignment with current regulatory requirements and recommendations.
- Apply the Food and Drug Administration's (FDA) recommendations in recently-issued guidance to industry.
- Describe FDA's approach to policies, regulations and inspection programs related to products regulated by the Center for Biologics Evaluation and Research (CBER).

Thank you!

***We appreciate the support of our AABB members
and the questions you submitted.***

We also appreciate the support of the
FDA and the
Centers for Medicare & Medicaid Services

Our FDA Attendees:

The following speakers have no financial disclosures:

- **Catherine McGraw BSN, RN**, Consumer Safety Officer, Center for Biologics Evaluation and Research (CBER), Office of Blood Research and Review (OBRR), Division of Blood Components and Devices (DBCD), Blood and Plasma Branch (BPB)
- **Carlos Villa, MD PhD**, Associate Director for Special Programs, CBER, OBRR

Our CMS Participants:

The following participants have no financial disclosures:

- **Daralyn Hassan, MS, MT(ASCP)**, Clinical Laboratory Scientist
Center for Clinical Standards and Quality (CCSQ), Quality, Safety &
Oversight Group (QSOG), Division of Clinical Laboratory Improvement and
Quality (DCLIQ)
- **Mary L. Hasan, MPA, MT(ASCP)**, Clinical Laboratory Scientist
CCSQ, QSOG, DCLIQ
- **Jelani R. Sanaa (She/Her), MS, MLS(ASCP)^{CM} SBB^{CM}, SH^{CM}**, Clinical
Laboratory Scientist CCSQ, QSOG, DCLIQ

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- 2021-2022 Regulatory Updates Toolkit – a searchable PDF of all Regulatory articles from Weekly Report
- 2019-2020 Regulatory Updates



ASK THE FDA

Blood and Blood Components

FDA Registration of Transfusion Services

Background: During the [2020 Ask the FDA Session](#), a question was asked regarding whether a Transfusion Service that re-labels red blood cell components with molecular antigen testing results based on testing performed by an Immunohematology Reference Laboratory (IRL) would need to register with FDA.

FDA's response was, *"Yes, labeling red cell components with molecular antigen test results is considered a manufacturing step, per [21 CFR 600.3\(u\)](#), that would require a facility to register in accordance with [21 CFR 607.7](#)."*

Question 1: Please clarify if a Transfusion Service must be registered if performing serological antigen testing on red blood cell units for compatibility testing. The result of this testing is documented in the Blood Establishment Computer System (BECS). The Transfusion Service does not re-label these units, they just add a sticker with the antigen-negative or antigen-positive results.



FDA/OBRR Q1:

“Per [21 CFR 607.65\(f\)](#), transfusion services that only perform compatibility testing are not required to register. Therefore, if a transfusion service performs serologic antigen testing as part of the compatibility test and does not re-label the units, it is not considered a manufacturing step that requires registration with FDA.”

Shipment Across State Lines

Background: FDA regulation [21 CFR 607.7](#) describes:

“Establishment registration and product listing of blood banks and other firms manufacturing human blood and blood products. All owners or operators of establishments that engage in the manufacturing of blood products are required to register, pursuant to Section 510 of the Federal Food, Drug, and Cosmetic Act. Registration and listing of blood products must comply with this part. Registration does not permit any blood bank or similar establishment to ship blood products in interstate commerce.”

Shipment Across State Lines (cont'd)

A registered-only hospital-based blood collection establishment ships RBC components to an in-state, FDA-licensed IRL for molecular antigen typing. The components are then re-labeled by the molecular testing facility with the antigen testing results. The license number of the molecular testing facility is included on the new label. The components are then returned to the hospital establishment. The hospital-based facility has developed this process because they do not want the responsibility of re-labeling the blood.



Shipment Across State Lines (cont'd)

Question 2: Can these components, labeled with the molecular testing facility license number, now be shipped across state lines?

FDA/OBRR Q2:

“No, the components labeled as described cannot be shipped across state lines. Blood and blood components must be licensed upon collection to be distributed in interstate commerce.”



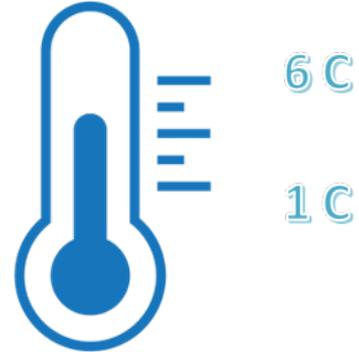
Transport of Blood

Background: [21 CFR 640.4\(h\)](#) provides the storage requirements for the collection of blood.

*“(h) **Storage**...If transported, the blood must be placed in temporary storage having sufficient refrigeration capacity to cool the blood continuously toward a temperature range between 1 and 10 °C until arrival at the processing laboratory. At the processing laboratory, the blood must be stored at a temperature between 1 and 6 °C. Blood from which a component is to be prepared must be held in an environment maintained at a temperature range specified for that component in the directions for use for the blood collecting, processing, and storage system approved for such use by the Director, CBER.”*

Transport of Blood (cont'd)

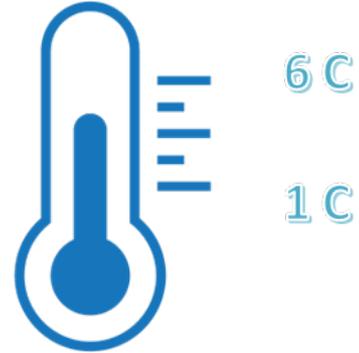
In our example, whole blood is transported from a collection center to a processing facility. The facility uses two types of bags: one for whole blood and one for leukoreduction post-transport. Filtering and component manufacturing is performed at room temperature before being placed in storage at 1-6 C. Currently, the products are transported in coolers with no ice with the understanding that they are cooling from body temperature towards 1-10 C. Platelets will not be manufactured from these components.



Question 3: Does this practice meet the requirements of [21 CFR 640.4\(h\)](#)?

FDA/OBRR Q3:

“No: If the intent is to store the blood at 1-10 C while it is transported, the blood must be placed in temporary storage having sufficient refrigeration capacity to cool the blood continuously toward a temperature range between 1 and 10 °C. Based on the information provided, your practice does not meet these requirements. It is unclear how a cooler without ice has been validated to maintain the required storage temperature. Transport containers/coolers must be validated to verify that they maintain proper temperature ranges specified for blood components while in transit, in accordance with [21 CFR 640.4\(h\)](#).”



Prior Approval Supplements

Background: [21 CFR 601.12](#) Changes to an approved application states:

“(b) Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).

(3) The applicant must obtain approval of the supplement from FDA prior to distribution of the product made using the change.”

We are a licensed blood establishment, applying for a Prior Approval Supplement (PAS) for pathogen-reduced platelets.

Question 4: Can the products for which the establishment is submitting the PAS, be distributed as unlicensed products within the state they are manufactured, with the license number removed from the label?

FDA/OBRR Q4:

“Yes: unlicensed pathogen-reduced platelets can be distributed in intrastate commerce (within the state in which the product is manufactured), as long as the U.S. license is obscured on the container label. Because the component is not licensed until the Prior Approval Supplement (PAS) is approved, it cannot be distributed in interstate commerce (outside the state of manufacture).”

Prior Approval Supplements (cont'd)

Background: Continuing with [21 CFR 601.12\(b\)\(2\)\(vi\)](#), a PAS is required for:

“Changes which may affect product sterility assurance, such as changes in product or component sterilization method(s), or an addition, deletion, or substitution of steps in an aseptic processing operation.”

Supply chain issues have led to many unexpected shortages of critical supplies. Our blood collection facility has been able to borrow or locate alternate supplies in many cases.

Question 5: Is a PAS needed when a licensed facility successfully completes a validation for a new arm scrub?



Prior Approval Supplements (cont'd)

FDA/OBRR Q5:

“No: Information regarding facility validation of a new arm scrub can be submitted in an Annual Report. Acceptable options for arm preparation methods would include antiseptic products that are intended for use for skin preparation prior to surgery or injection, or that have a blood donor collection claim in the package insert or manufacturer’s instructions.”

Donor Classification

Background: According to FDA's [Compliance Policy Guide CPG Sec. 230.150: Blood Donor Classification Statement, Paid or Volunteer Donor](#), III. Policy page 4:

“B. Volunteer Donors

Other examples of incentives that would not require the “paid donor” classification are described in the preamble to the final regulation (43 FR at 2142-43). These include 1) lotteries or raffles, regardless of the value of the prize to be given away;”

Question 6: Would it be acceptable to host a blood drive at a marijuana dispensary where the raffle prize for blood donation is a \$500 gift certificate to the dispensary?



Donor Classification (cont'd)

FDA/OBRR Q6:

“Yes: Blood donations collected from donors who meet all donor eligibility requirements and are offered incentives such as “lotteries or raffles, regardless of the value of the prize to be given away,” do not require paid donor labeling, if the prize is not readily convertible to cash. You may refer to FDA’s Compliance Policy Guide [CPG Sec. 230.150](#), dated December 2019. A link will be provided for today’s transcript. (<https://www.fda.gov/media/75039/download>).”

Therapeutic Phlebotomy

Background: [21 CFR 630.15\(a\)\(2\)](#) provides the regulations for therapeutic phlebotomy:

“(2) When a donor who is determined to be eligible under [§ 630.10](#) undergoes a therapeutic phlebotomy under a prescription to promote the donor's health, you may collect from the donor more frequently than once in 8 weeks...provided that the container label conspicuously states the disease or condition of the donor that necessitated phlebotomy. However, no labeling for the disease or condition is required under this section if:



Therapeutic Phlebotomy (cont'd)

- i) *The donor meets all eligibility criteria;*
- ii) *The donor undergoes a therapeutic phlebotomy as prescribed by a licensed health care provider treating the donor for:*
 - (A) *Hereditary hemochromatosis;*
 - (B) *Another disease or condition, when the health of a donor with that disease or condition will not be adversely affected by donating, and the donor's disease or condition will not adversely affect the safety, purity, and potency of the blood and blood components, or any products manufactured from them, and the collection is in accordance with a procedure that has been found acceptable for this purpose by FDA; and*
- iii) *You perform without charge therapeutic phlebotomies for all individuals with that disease or condition.”*

Therapeutic Phlebotomy (cont'd)

In our first example, a long-time allogeneic donor now presents to the donation center and states, “My doctor told me I have hemochromatosis and I needed to come donate blood.” The donor otherwise meets the requirements of [21 CFR 630.10](#) and does not need to donate more frequently than every 8 weeks.

Question 7: Is a prescription needed for an individual with hereditary hemochromatosis, who meets the eligibility requirements of [21 CFR 630.10](#) but does not require phlebotomy more frequently than every 8 weeks?

FDA/OBRR Q7:

“The responsible physician in the blood center must determine if a donor with a specific medical condition is eligible to donate blood ([21 CFR 630.10\(e\)](#)). From what you have described, the donor is not presenting for a therapeutic phlebotomy.

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Therapeutic Phlebotomy (cont'd)

FDA/OBRR Q7: (cont'd)

A prescription is not required for an individual with hereditary hemochromatosis who meets all eligibility requirements under [21 CFR 630.10](#) and [21 CFR 630.15](#) and does not require phlebotomy more frequently than every 8 weeks.”

Question 8: If no prescription is required, is labeling for the disease or condition required?

FDA/OBRR Q8:

“No, in this scenario the donor is not presenting for therapeutic phlebotomy under a doctor’s prescription, therefore, labeling for the disease or condition is not required for donors with Hereditary Hemochromatosis who meet all donor eligibility requirements described in [21 CFR 630.10](#).”

Therapeutic Phlebotomy (cont'd)

In our second example, a first-time donor presents for donation and meets the eligibility criteria in [21 CFR 630.10](#). During the phlebotomy the donor states “I have too much blood. I have something called polycythemia.”

Question 9: If the collection facility labels the blood components conspicuously stating that the donor has polycythemia, can this blood be transfused as an allogeneic product?



FDA/OBRR Q9:

“It is not clear in this example if the donor is eligible or if the component is suitable for transfusion.

The responsible physician in the blood center must determine if a donor with a specific medical condition is eligible to donate blood ([21 CFR 630.10\(e\)](#)). Evaluation of a donor’s eligibility to donate blood includes several questions about different medical conditions, such as cancer.

If the unit was already collected, the responsible physician must determine if the blood product is suitable as required under [21 CFR 630.30\(a\)](#).”

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Therapeutic Phlebotomy (cont'd)

FDA/OBRR Q9 (cont'd):

Polycythemia, or too many red blood cells, may be a primary disorder (e.g., polycythemia vera, which is a type of blood cancer (hematologic malignancy), or secondary to other causes, such as smoking or high altitude. FDA is aware that the practice in most blood centers is to defer individuals with conditions such as polycythemia vera and other blood cancers permanently, and not distribute blood collections from such donors for transfusion.”

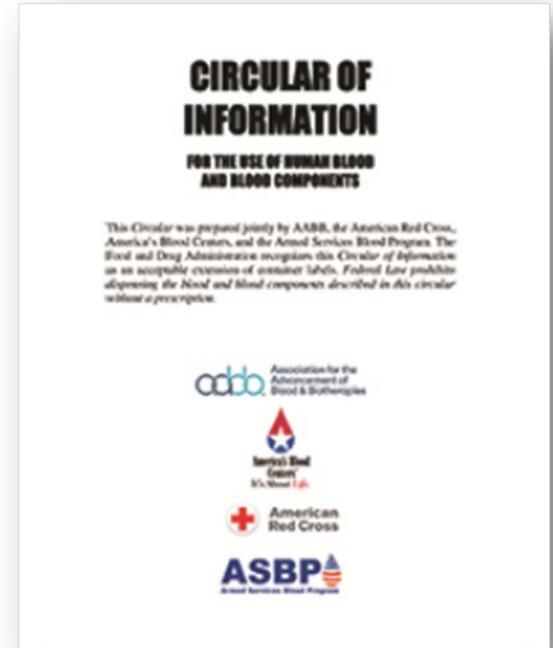
Circular of Information

Background: [21 CFR 606.122 Circular of information](#) states:

“A circular of information must be available for distribution if the product is intended for transfusion.”

During the [2017 Ask the FDA session](#), the agency clarified:

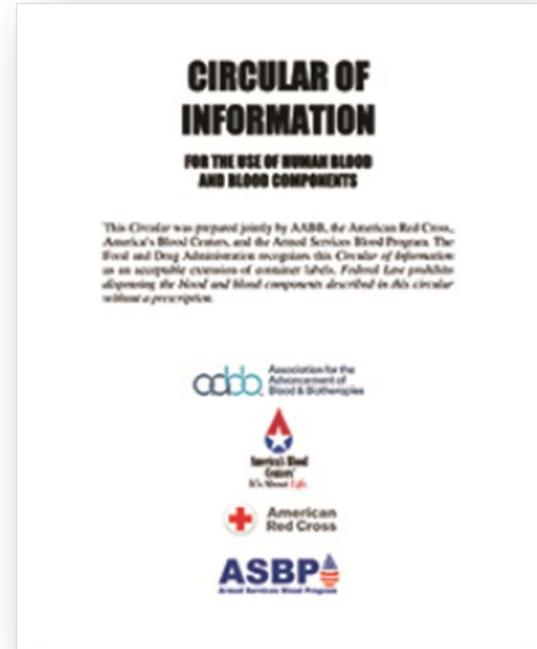
“If the environment includes blood transfusion, the Circular should be available.”



Question 10: Does the *Circular of Information* and all labeling requirements apply to the collection and transfusion of perioperative blood when reinfusion or use of a component occurs during the same surgical procedure?

FDA/OBRR Q10:

“No, the Circular of Information labeling requirements in [21 CFR 606.122](#) do not apply to perioperative autologous blood collections, or other autologous re-infusion procedures during surgery.”



Background: The [1993 Memorandum on Irradiation](#), Section III.C Radiation Dosages and Validation states *“Use of indicator devices, which signal exposure of the blood product container to radiation, is encouraged.”* Section E.1 Labeling states, *“Irradiated blood product containers should be permanently labeled as irradiated.”*

Following irradiation, it is discovered that a RadSure sticker had not been applied to a unit of red blood cells as required by our policy.

Question 11: Can this unit of red blood cells, labeled with the appropriate expiration date based on the assumption that it had been irradiated, be returned to inventory not labeled as irradiated or must the component be discarded?

**IRRADIATE
ALL PRODUCTS**

FDA/OBRR Q11:

“Yes, since you are uncertain about whether the red blood cell unit was irradiated, we agree that you can change the expiration date based on the assumption that the unit was irradiated, and you should not label the unit as irradiated when you return it to inventory for transfusion to patients who do not require irradiated blood products. As a precaution, the expiration date should be changed to 28 days after irradiation if remaining shelf life exceeds 28 days.”

Sterile Connecting Device (STCD)

Background: The 2000 [Guidance for Industry: Use of Sterile Connecting Devices in Blood Bank Practices](#), **Section II. Recommendations, Section D. Using the STCD to prepare an aliquot for pediatric use and divided units**, page 4 states SOPs should include descriptions of:

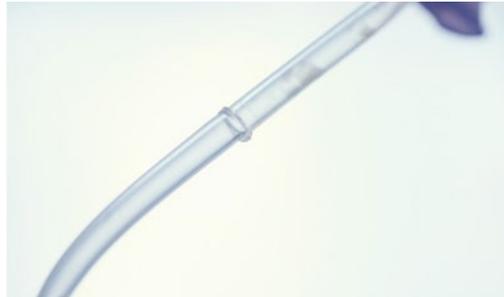
“...storage time of the product. The product should be in an approved container and should be consistent with the storage time on the label of such container...”

A transfer pack package insert states, *“For processing and/or storage of blood or blood components.”* No other information on specific component types is provided nor is there information on storage time or expiration dating.

Sterile Connecting Device (STCD) (cont'd)

Question 12: Assuming an acceptable weld is achieved, does this statement mean any “blood and blood component” may be stored in this bag including red cells, plasma components destined for storage at $<18^{\circ}$ C, thawed plasma and platelets?

Question 13: Again, assuming an acceptable sterile weld is achieved, when the package insert for the Transfer Pack Container does not describe a storage time or expiration date, can we assume the component retains the original expiration?



Sterile Connecting Device (STCD) (cont'd)

In our next example, again assuming an acceptable sterile weld, the transfusion service aliquots RBCs (or platelets) into a syringe and issues the syringe to an operating room in a validated cooler where it is available for the duration of the surgery. The package insert for the sterile syringe does not state, “For processing and/or storage of blood or blood components” and does not provide storage time limits.

Question 14: Can this container be used for aliquoting and storage of red blood cells and/or platelets as described in this example?

Question 15: If yes, would the products retain their original expiration?



Sterile Connecting Device (STCD) (cont'd)

FDA/OBRR Q12-15:

“Consolidated answer to questions 12-15: For transfer packs and/or syringes, we recommend you review and follow the manufacturer’s package insert/instructions for use or consult directly with the manufacturer of the device regarding aliquoting, processing, storage, and expiration times of specific blood products.

FDA regulations do not specifically address aliquoting, processing, and storage of Red Blood Cells (RBCs) in syringes. We have cleared some pediatric syringes to be used to prepare and deliver aliquots of blood products for transfusion. Please review your syringe manufacturer’s package insert regarding storage and expiration times of specific blood products. We are aware a commonly used expiration time frame for syringe aliquots of refrigerated (1-6°) RBCs in some hospital blood banks/transfusion services is up to 24 hours.”

Platelet Bacterial Risk Guidance

Background: The December 2020 [Platelet Bacterial Risk Control Guidance](#) provides the recommendations for culture strategies to label apheresis platelets with either a 5-day expiration or a 7-day expiration.

We are a hospital-based blood collection establishment with access to component disposition from our transfusion service. Once we have confirmed that all parts of a platelet component have been transfused, we plan to discard the culture bottles to free up room in our incubators. This discard will occur the following morning.



For example, a single unit apheresis product labeled with a 7-day expiration is transfused on day 4. We would discard the culture bottles associated with that component the next morning. The guidance document does not describe whether the bottles must be incubated and monitored for the entire expiration life of the product.

Question 16: Is it acceptable to discard the bottles once the transfusion has been confirmed?

FDA/OBRR Q16:

“No. You must follow the instructions in the manufacturer’s package inserts for the FDA-cleared culture devices being used in your testing, in accordance with [21 CFR 606.65\(e\)](#). The package inserts for currently cleared bacterial culture devices intended for use in quality control testing of platelet components recommend culture of 5 to 7 days, or until component outdate, which may facilitate investigation of possible septic transfusion reactions.”

Treponemal Screening Tests

Background: [21 CFR 610.40\(h\)\(2\)\(vi\)](#) provides an exception to distribute human blood or blood components that test reactive by a screening test for syphilis and further tested by an adequate and appropriate test that demonstrates the reactive test is a biological false-positive. The [December 2020 Guidance document](#), Recommendations for Screening, Testing, and Management of Blood and Blood Components Based on Screening Tests for Syphilis, includes wording in the footnote on page 9 that states that the FDA does not consider negative results on an additional Treponemal test to be indicative of biological false-positives on the screening test. The footnote goes on to state that regardless of the result from the additional Treponemal screening test, you must not release the index donation unless an exception in [21 CFR 610.40\(h\)](#) applies. A related question is donor notification for a reactive Syphilis screening test: [21 CFR 630.40\(a\)](#) requires notification when the donor has been deferred based on the results of tests for evidence of infection with a relevant transfusion-transmitted infection.

Question 17: When performing a Treponemal initial screening test, what is the rationale for not considering a second method Treponemal test an option to identify a biological false-positive?

FDA/OBRR Q17:

“Treponemal assays are specific and detect antibodies against the spirochete (*Treponema pallidum*) that causes syphilis, and do not give biological false positive results.

Only nontreponemal (nonspecific) screening tests occasionally result in biological false positive results, usually when the donor has certain underlying diseases or condition (see #2 below). The result of the nontreponemal screening test can be considered a biological false positive, when the reactive nontreponemal screening test result is followed by a non-reactive treponemal test result.”

Question 18: What would qualify for a test that demonstrates the initially reactive screening test is a biological false-positive?

FDA/OBRR Q18:

“Only a nontreponemal screening test can have results interpreted as a biological false positive, which occurs when a reactive nontreponemal screening test result is followed by a nonreactive treponemal test result.”

“Biological false-positive reactions occur occasionally with the non-treponemal antigen. Such reactions sometimes occur in samples from individuals with a history of drug abuse, pregnancy, or with diseases such as lupus erythematosus, malaria, vaccinia, mononucleosis, leprosy, viral pneumonia, and after smallpox vaccinations.”

Treponemal Screening Tests (cont'd)

Question 19: As we automatically reflex a second method Treponemal test and have both results available when evaluating the donor for deferral, is notification required as a deferral is not assigned to the donor when the second test is nonreactive on the index sample?

FDA/OBRR Q19:

“Because the donor is eligible for reentry on subsequent donation and no longer deferred based on the second (different) treponemal test, donor notification is not required. Please note that the donation with initially reactive results for treponemal antibodies must be discarded.

For additional information, please refer to the guidance *‘Recommendations for screening, testing and management of blood donors and blood components based on screening test for Syphilis’* dated December 2020.”

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-screening-testing-and-management-blood-donors-and-blood-and-blood-components-based>

Record Retention

Background: [21 CFR 606.160](#) describes Record Retention requirements and records of deferred donors:

“(d)...When there is no expiration date, records shall be retained indefinitely”

“(e)(2) Establishments must maintain at all locations operating under the same license or under common management a cumulative record of donors deferred from donation under [§ 610.41 of this chapter](#) because their donation tested reactive under [§ 610.40\(a\)\(1\) of this chapter](#) for evidence of infection due to HIV, HBV, or HCV.”



Question 20: For those records that require an indefinite or cumulative retention, must those records be retained if we can confirm that the donor or recipient is deceased?

FDA/OBRR Q20:

“Yes, product records must be retained indefinitely when the product has no expiration date. However, we are not aware of products without expiration dates, so this requirement for retaining records indefinitely is likely limited in its applicability.”



BECS Updates

Background: The 2013 FDA Guidance, [Blood Establishment Computer System Validation in the User's Facility](#) provides the following:

“Due to the complexity of systems and BECS, a seemingly small local change (e.g., software, hardware, peripherals, or infrastructure) may have a significant global system effect. When any change (even a small change) is made to the software on the system, a software regression analysis should be conducted, not just for validation of the individual change, but also to determine the extent and impact of that change on the entire system.”

Question 21: Can the FDA comment on how they would view an update to blood bank vendor software to allow that software to exchange red blood cell alloantibody data across systems, via the proposed US-wide red blood cell alloantibody exchange?
(www.alloantibody.org)

Question 22: Would this be a big enough change to the software to require FDA re-evaluation?

FDA/OBRR Q21-22:

“It is unclear if this question is from a BECS manufacturer’s or from an end user’s perspective. We provide separate responses for BECS manufacturers and end users.

BECS Manufacturers:

From the information you provided it’s unclear how the alloantibody exchange information will be used by the Blood Donor Centers and Transfusion Services, or if the change will augment the performance of the BECS device or to expand or modify BECS’ indications for

(continued on next slide)

FDA/OBRR Q21-22 (cont'd):

use. BECS manufacturers should perform a risk-based assessment that compares the modified device to the most recent 510(k) cleared device to determine if the change is significant and new 510(k) is needed. We recommend that manufacturers submit a pre-submission meeting via the Q-submission Program for FDA's feedback.

End users:

We recommend that you contact your BECS manufacturer to develop your validation plan. A risk assessment should be performed to determine the degree of validation required based on the identified risks of the software change.”

Administration of Blood

Background: At our hospital, therapeutic apheresis procedures are performed by Medical Technologists or Medical Laboratory Technicians. They have been qualified by training and competency assessment and follow policies and procedures which have been reviewed and approved by the Transfusion Services medical director. Training includes the recognition of adverse events related to transfusion. They administer blood products and medications prescribed by the patient's physician during the procedure. The patient's nurse is available for patient care needs.

Question 23: We want to make sure we are in compliance with FDA regulations. Are there federal regulations or guidance describing who can administer blood products?

Administration of Blood (cont'd)

FDA/OBRR Q23:

“FDA regulations do not define requirements or describe who can administer blood products. Your hospital should determine the proper policy and procedures for administration of blood and blood components. You may consider referencing AABB standards, CAP, Joint Commission, and CMS requirements as well.”

Red Blood Cell Loss

Background: In reviewing the [December 2007 Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods](#), the Guidance does not differentiate the accounting of losses due to non-reinfusion events and normal routine red cell events when assessing RBC losses in the last 8 weeks when a non-reinfusion event occurs.

- “VII. Quality Assurance and Monitoring, B.3. Red Blood Cell Loss, page 17:*
- *Donor eligibility based on RBC loss (with or without RBC rinseback and including all other types of donation) is described in Table 2.”*

However, in the [2011 Ask the FDA](#), Question 27, FDA described and provided an example where the normal routine red cell loss is not included in the calculation of the deferral period after non-reinfusion event.

Red Blood Cell Loss (cont'd)

“As for the example here, I think I need to clarify something for this author. The 200 mL and 300 mL red cell loss criteria that are in the apheresis guidance documents – both “Collection of Platelets by Automated Methods” and the “Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods” applies only to incomplete procedures from those devices for those products. So, it doesn’t account for normal routine red cell loss.”

The Guidance and the 2011 Ask the FDA transcript response appear to be in conflict.

Question 24: Can FDA please clarify the expectation for industry for compliance with tracking RBC loss of after an incomplete reinfusion event?

Red Blood Cell Loss (cont'd)

FDA/OBRR Q24:

“Red Blood Cells losses due to incomplete reinfusion events, when Red Blood Cells cannot be returned to the donor, must be included in tracking the total Red Blood Cell loss for a donor over time. Tracking is done to ensure that the total red cell loss in any 8-week period is not greater than would occur due to a routine collection of a single unit of Whole Blood which requires an 8-week deferral. In addition, you must defer a donor for 8 weeks or more, if the cumulative red blood cell loss in any 8-week period, could adversely affect the donor’s health, per [21 CFR 630.15\(b\)\(6\)](#).”

Equipment – Standardized and Calibrated

Background: [21 CFR 606.60\(b\)](#) provides a list of equipment that shall be observed, standardized and calibrated with a specified frequency. A general lab centrifuge is included in this list of equipment.

Question 25: Please clarify which of these is considered a "general lab centrifuge?"

- A centrifuge used to manufacture blood components
- A centrifuge used to perform serological testing
- A centrifuge used to spin down specimens to separate serum/plasma from RBCs for clinical laboratory testing

FDA/OBRR Q25:

“All three (3) types of centrifuges listed may be considered general laboratory centrifuges and should be observed, standardized, and calibrated according to the frequency listed in [21 CFR 606.60\(b\)](#).”

Source Plasma – Product Specific Guidelines

Background: [21 CFR 640.65\(b\)](#) provides the procedure-specific requirements for Source Plasma collected by plasmapheresis:

“(1)(i) Except as provided under [§ 630.25 of this chapter](#), the responsible physician must draw a sample of blood from each donor on the day of the initial physical examination or plasmapheresis, whichever comes first, and at least every 4 months thereafter. A serologic test for syphilis, a total plasma or serum protein determination, and a plasma or serum protein electrophoresis or quantitative immuno-diffusion test or an equivalent test to determine immunoglobulin composition of the plasma or serum shall be performed on the sample.”

Source Plasma – Product Specific Guidelines (cont'd)

Question 26: What is required as part of the submission for a quantitative immune-diffusion test or an equivalent test to determine immunoglobulin composition? Would the submission be an Annual Report as indicated in Appendix K of the December 2014 [Guidance for Industry-Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture?](#)

FDA/OBRR Q26:

“Licensed Source Plasma establishments should submit implementation of a new test for immunoglobulin composition consistent with the manufacturer’s instructions as an Annual Report per [21 CFR 601.12\(d\)](#). The submission must include the name of the laboratory performing the test and name of the FDA cleared/approved test and manufacturer. You may refer to Appendix K of [‘FDA Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture’](#) dated December 2014.”

Source Plasma - Inspections

Background: During recent, routine FDA field investigations at Source Plasma facilities, inspectors have issued affidavits to the facility being inspected. In most instances there has been an FDA training supervisor present when the affidavit is issued. However, it has occurred with inspections led by one investigator. When questioned, the field investigator implied that the affidavit issuance was part of a training exercise.

Question 27: Can FDA comment on the circumstances in which an affidavit is warranted, the intent of an affidavit, and elaborate if there have been any recent changes in the compliance and surveillance programs in place?

Check back for FDA's response to this question.



ASK THE FDA

Cellular Therapy

Biological Product Deviation (BPD) Reporting

Dr. Khuu was not able to join us for today's recording. As is our practice, we will provide Dr. Khuu's responses in the transcript for this session. Look for a Weekly Report article in the coming weeks announcing that the transcript has been posted on our website: [Ask the FDA & CLIA Transcripts](#)

Background: A small autologous hematopoietic progenitor cell (HPC) lab's current practice when receiving notification of a positive culture is to document and then repeat the culture. If the second culture comes back negative it will then be reported out as negative. In most cases, the positive growth is a single colony and chalked up to plate contamination. If the second culture is positive, an additional culture would be performed to determine where contamination may have occurred within the process. The laboratory only reports a BPD to FDA for a product with a repeat positive culture.

Biological Product Deviation (BPD) Reporting

Question 1: How should these situations be handled?

Is FDA reporting necessary if:

- The product was administered?
- The product was distributed, but not administered?
- The product was not administered?
- Are there additional plausible scenarios where FDA reporting is required?

FDA/OTAT Q1:

“An HCT-P deviation report is required if the culture is positive, regardless of whether additional cultures were negative, and the product was distributed. Deviation reporting is not dependent upon whether the product was administered.”

Biological Product Deviation (BPD) Reporting (cont'd)

The [FDA March 2020 BPD Guidance](#) states you are not required to submit a report to the FDA when you detected a deviation and, prior to distribution, you made appropriate corrections following appropriate procedures.

Question 2: How would this apply to a scenario where there is a positive culture, if at all?

FDA/OTAT Q2:

“The guidance referenced is specific to deviation reporting for blood establishments. The guidance document for HCT/P deviation reporting, [Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-Based Products Regulated Solely Under Section 361 of the Public Health Service Act and 21 CFR Part 1271; Guidance for Industry](#), provides the same example of a non-reportable event.

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Biological Product Deviation (BPD) Reporting (cont'd)

FDA/OTAT Q2 (cont'd):

This scenario does not apply to events in which there is a positive culture. It only applies to deviations that were detected and corrected prior to distribution; for example, a missing RCDAD test result was detected prior to distribution but an appropriate sample was available for testing. Testing was performed and was acceptable before the product was distributed.”

Timing of Specimen Collection

Background: [21 CFR 1271.80\(b\)](#) provides the requirements for timing of specimen collection of Human Cells, Tissues, and Cellular and Tissue-Based Products:

“(b) You must collect the donor specimen for testing at the time of recovery of cells or tissue from the donor; or up to 7 days before or after recovery, except:

(1) For donors of peripheral blood stem/progenitor cells, bone marrow (if not excepted under [§ 1271.3\(d\)\(4\)](#)), or oocytes, you may collect the donor specimen for testing up to 30 days before recovery;”

Question 3: Is there a reference which explains the basis for a 30-day window for collection of the donor specimen for testing of HPC-apheresis and HPC-marrow, and a different 7-day window for HPC-cord blood?

Timing of Specimen Collection (cont'd)

FDA/OTAT Q3:

“Yes, we refer you to:

1. Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, Final Rule, May 25, 2004: [69 FR 29785](#)
2. Human Cells, Tissues, and Cellular and Tissue-Based Products; Donor Screening and Testing, and Related Labeling, “Interim Rule” May 25, 2005: [70 FR 29952](#)
3. Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, August 2007, section V.E

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Timing of Specimen Collection (cont'd)

FDA/OTAT Q3 (cont'd):

The Donor Eligibility final rule can be accessed at www.federalregister.gov. Refer to this excerpt from a response in the preamble:

Since the recipient (of peripheral blood stem/progenitor cells) undergoes a myeloablative treatment regiment, i.e., high dose chemotherapy and total body irradiation, it is important to determine the eligibility of the donor before the recipient's treatments begin. At 7 days prior to recovery, the treatment of the recipient has already started and the decision to proceed is irreversible. Therefore, under § 1271.80(b), for donors of peripheral blood stem/progenitor cells only, the establishment may collect the donor specimen up to 30 days before recovery of the stem/progenitor cells. We understand that the current practice of peripheral blood stem/progenitor cell establishments is to take a donor specimen on the day of recovery for additional testing, and we encourage these establishments to continue this practice, in order to permit appropriate follow-up and treatment if test results are positive.

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Timing of Specimen Collection (cont'd)

FDA/OTAT Q3 (cont'd):

The Interim Rule addresses bone marrow: Refer to this excerpt from a response in the preamble:

In the donor eligibility final rule we state that we permit collection of the donor specimen up to 30 days before recovery for donors of peripheral blood stem/progenitor cells due to the myeloablative treatment regimen and the need to determine the eligibility of the donor before the recipient's treatment begins (69 FR 29786 at 29808). Because this reasoning also applies to donors of bone marrow covered by the HCT/P regulations and donors of oocytes who must undergo conditioning regimens beginning more than 7 days before recovery of oocytes, we have included a reference to bone marrow and oocytes in § 1271.80(b) to permit testing up to 30 days before recovery.

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Timing of Specimen Collection (cont'd)

FDA/OTAT Q3 (cont'd):

The 2007 HCT/P Donor Eligibility guidance document can be accessed on FDA/CBER's Tissue and Tissue Products webpage under Tissue Guidances <https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/tissue-guidances>. See section V. listing E:

V. DONOR TESTING: GENERAL (§ 1271.80)

E. When do I collect a specimen for testing?

You must collect the donor specimen for testing at the same time as cells or tissue are recovered from the donor, or within seven days before or after the recovery of cells and tissue (§ 1271.80(b)), with some exceptions as described in this section.

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FDA/OTAT Q3 (cont'd):

In the case of donation of hematopoietic stem/progenitor cells (HPCs) obtained from peripheral blood or bone marrow (if not excepted under 1271.3(d)(4)), we realize that the recipient may begin myeloablative chemotherapy more than 7 days before the transplant. Therefore, the identified allogeneic donor might need to be qualified before this time, including screening and testing of the donor for relevant communicable diseases. In this situation, you may collect the donor specimen used for communicable disease testing up to 30 days before donation (1271.80(b)(1)).

In summary, the 30-day period in 21 CFR 1271.80(b)(1) applies to donors of HPC – Apheresis and bone marrow (if not excepted) due to medical and clinical considerations but the same considerations are not applicable to donors of HPC - Cord Blood.”

Storage of an Autologous Craniotomy Bone Flap

Background: Procurement is performed during the craniotomy procedure and stored until the patient has a second procedure: a cranioplasty to implant the stored bone. These procedures are possibly months apart and not during the same procedure where the bone was removed to allow room for brain swelling. Although the processing is minimal, the bone is stored in a freezer until it is distributed for the second surgery.

Question 4: Does storage of autologous craniotomy bone flap require FDA registration?

FDA/OTAT Q4:

“According to [§1271.15\(b\)](#), you are not required to comply with the requirements in [21 CFR part 1271](#) if you are an establishment that removes human cells, tissues, or cellular or tissue-based products (HCT/Ps) from an individual and implants such HCT/Ps into the same individual during the same surgical procedure. An establishment that qualifies for

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Storage of an Autologous Craniotomy Bone Flap (cont'd)

FDA/OTAT Q4 (cont'd):

the exception in [§1271.15\(b\)](#) is not required to register with the FDA or comply with [21 CFR part 1271](#) provided they do not manufacture any other HCT/P.

Regarding autologous cranial bone flap, you may refer to the [Guidance for Industry: Same Surgical Procedure Exception under 21 CFR 1271.15\(b\): Questions and Answers Regarding the Scope of the Exception](#) (SSPE Guidance) (November 2017) for additional information. Specifically, as explained in Question & Answer #6, an establishment that performs craniotomy or craniectomy with subsequent implantation of the autologous bone flap in the same individual to reverse the cranial defect generally would qualify for the exception in [§1271.15\(b\)](#), even though the removal and future implantation may be a number of days apart. During this time, the cranial bone flap may be rinsed or cleansed and temporarily stored after being labeled, pending implantation, and this would still be

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Storage of an Autologous Craniotomy Bone Flap (cont'd)

FDA/OTAT Q4 (cont'd):

considered the same surgical procedure, provided no other processing steps and no other manufacturing steps beyond labeling and storage are performed. You may refer to the SSPE guidance referenced above for additional information on bone flaps.

For the scenario you describe, the hospital would qualify for the exception under [§1271.15\(b\)](#), if they recover autologous cranial bone flap, take steps to preserve the tissue in an appropriate condition for temporary storage and future implantation at their hospital.

The exception generally applies only to those establishments that both remove and implant the autologous HCT/P at the same establishment. Please note that for craniotomy or craniectomy procedures, Question & Answer #6 further explains that under limited circumstances in order to accommodate the medical needs of an individual patient, there

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Storage of an Autologous Craniotomy Bone Flap (cont'd)

FDA/OTAT Q4 (cont'd):

may be a medical necessity for the establishment that removed the autologous cranial bone flap to send the HCT/Ps to a different establishment for reimplantation in the patient. In such cases, provided precautions will be taken to protect the HCT/P from contamination and cross contamination, FDA does not intend to object to the recovering establishment sending the autologous cranial bone flap to a different establishment for reimplantation in the patient, without registering and listing with the FDA.

We understand non-government organizations such as The Joint Commission (TJC) have accreditation programs for hospitals and other health care facilities, including standards and “Elements of Performance” for safe handling of human tissues for transplant. For example, TJC standards include requirements for tracking and managing human tissue products. You may refer to their [website](#) for these standards.”

Vendor-Purchased Biological Products

Background: We are a Level One Trauma Center, so we store a variety of bone and dermis products. On occasion, one of our other facilities may request a product for an unplanned surgical patient or their product may have been contaminated during surgery and they need another product. We have used a *Deviation Authorization process with surgeon and Medical Director sign off to document the urgent need.*

Question 5: Is FDA registration required to ship biological products to another facility emergently for eminent surgical use? Is the Deviation Authorization sufficient or do we need to register with FDA?

FDA/OTAT Q5:

“Establishments that manufacture HCT/Ps regulated solely under section 361 of the Public Health Service Act and the regulations in [21 CFR part 1271](#) (361 HCT/Ps) are required to register and list their HCT/Ps with the FDA ([§1271.1\(b\)\(1\)](#)).

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Vendor-Purchased Biological Products

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FDA/OTAT Q5 (cont'd):

A number of exceptions from the requirements are listed in [§1271.15](#). Specifically, according to [§1271.15\(d\)](#), you are not required to comply with the requirements of [21 CFR part 1271](#), if you are an establishment that doesn't recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/Ps solely for implantation, transplantation, infusion, or transfer within your facility.

Establishment means a place of business under one management, at one general physical location, that engages in the manufacture of HCT/Ps ([§1271.3\(b\)](#)). One general physical location could be reasonably construed to include separate buildings within close proximity provided that the activities in them are closely related to the same business enterprise, under the supervision of the same local management, and capable of being inspected at the same time.

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Vendor-Purchased Biological Products

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FDA/OTAT Q5 (cont'd):

For the scenario you describe, it is unclear whether the level one trauma center and the “other facilities” are under the same management (e.g., same hospital system), are in close proximity (e.g., buildings on the same campus), and meet the “one general physical location” condition under [§1271.3\(b\)](#).

If the trauma center and “other facilities” are in close proximity (e.g., buildings on the same campus) and are under the same management, transfer of HCT/Ps between these facilities is not considered distribution as defined in [§1271.3\(b\)](#). Registration with the FDA is not required, provided that they do not perform any other manufacturing steps as defined in [§1271.3\(e\)](#).

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Vendor-Purchased Biological Products

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FDA/OTAT Q5 (cont'd):

If the trauma center and “other facilities” are not in close proximity or are not under the same management, transfer of HCT/Ps from the trauma center to the “other facilities” would not meet the “one general physical location” condition under [§1271.3\(b\)](#) and the “within your facility” condition described in [§1271.15\(d\)](#). In such a case, the establishment that receives and subsequently transfers the HCT/P to another hospital is required to register and list all the HCT/Ps and manufacturing steps it performs, including storage and distribution. The registered establishment must comply with all applicable regulations in [21 CFR part 1271](#), including permitting establishment inspection by FDA (see [§1271.400](#)).”

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ASK CMS/CLIA

Proficiency Testing

Background: A facility recently discontinued performing red cell antibody detection testing (donor plasma tested against reagent red cells) and compatibility testing (patient plasma tested against donor red cells). For this reason, the facility discontinued subscribing to proficiency testing for these assays and removed them from their CLIA testing license profile.

During a recent inspection and review of proficiency testing results, it was noted Direct Antiglobulin Testing (DAT) and red cell antigen typing were being performed by the facility. The inspector stated that Antibody Detection and Compatibility testing (respectively) need to be listed on the CLIA license for performing these assays.

Question 1: Where in the CMS regulations is it specifically defined which assays are considered to be part of another test profile and need to be present on the CLIA license?

CMS Response Q1:

“CLIA does not have a definition of compatibility testing but follows the FDA definition. FDA’s definition of compatibility testing is the mixing of donor cells with patient serum. Based on the FDA definition, CLIA considers the mixing of donor cells with patient serum compatibility testing to fall under CLIA. For CLIA certification purposes, those laboratories performing red cell antigen typing, must be certified in the subspecialty of Compatibility Testing 550 in order to perform antigen typing/antigen confirmations. For CLIA certification purposes, those laboratories performing Direct Antiglobulin Testing (DAT), must be certified in the subspecialty of Antibody Detection (transfusion) 520 in order to perform DAT. This conforms with the instructions on the CMS-116.

Proficiency Testing (cont'd)

CMS Response Q1 (cont'd):

Below is a link to the CMS 116 form:

<https://www.cms.gov/Medicare/CMS-Forms/CMS-Forms/Downloads/CMS116.pdf>

SPECIALTY / SUBSPECIALTY	ACCREDITING ORGANIZATION	ANNUAL TEST VOLUME	SPECIALTY / SUBSPECIALTY	ACCREDITING ORGANIZATION	ANNUAL TEST VOLUME
HISTOCOMPATIBILITY 010			HEMATOLOGY 400		
<input type="checkbox"/> Transplant			<input type="checkbox"/> Hematology		
<input type="checkbox"/> Nontransplant			IMMUNOHEMATOLOGY		
MICROBIOLOGY			<input type="checkbox"/> ABO Group & Rh Group 510		
<input type="checkbox"/> Bacteriology 110			<input type="checkbox"/> Antibody Detection (transfusion) 520		
<input type="checkbox"/> Mycobacteriology 115			<input type="checkbox"/> Antibody Detection (nontransfusion) 530		
<input type="checkbox"/> Mycology 120			<input type="checkbox"/> Antibody Identification 540		
<input type="checkbox"/> Parasitology 130			<input type="checkbox"/> Compatibility Testing 550		
<input type="checkbox"/> Virology 140			PATHOLOGY		
DIAGNOSTIC IMMUNOLOGY			<input type="checkbox"/> Histopathology 610		
<input type="checkbox"/> Syphilis Serology 210			<input type="checkbox"/> Oral Pathology 620		
<input type="checkbox"/> General Immunology 220			<input type="checkbox"/> Cytology 630		
CHEMISTRY			RADIOBIOASSAY 800		
<input type="checkbox"/> Routine 310			<input type="checkbox"/> Radiobioassay		
<input type="checkbox"/> Urinalysis 320			CLINICAL CYTOGENETICS 900		
<input type="checkbox"/> Endocrinology 330			<input type="checkbox"/> Clinical Cytogenetics		
<input type="checkbox"/> Toxicology 340			TOTAL ESTIMATED ANNUAL TEST VOLUME:		

Question 2: How can we determine in which Specialty/Subspecialty category a laboratory test is categorized?

CMS Response Q2:

“The FDA’s Center for Devices and Radiological Health (CDRH) is responsible for CLIA Test Categorization. You may contact CDRH directly at: CLIA@fda.hhs.gov

FDA Text complexity database:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm>

The FDA’s CLIA website is provided below for your information and convenience.

<https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia>”

Background: We have personnel who may travel to another laboratory to perform testing. We use [42 CFR 493.1451\(b\)\(8\)](#) that lists the six methods that must be used for competency assessment. We have an electronic learning management system that tracks completed training and completed competency assessment for all testing staff in all laboratories. Prior to staff traveling to another laboratory to perform testing, the Laboratory Director/Designee accesses the electronic system to confirm that the staff member has the appropriate training and has a current successful competency assessment. After confirmation of the training and competency assessment results, the Laboratory Director signs that the staff can perform testing in his/her laboratory. In addition, all staff in the laboratories have direct access to our electronic document management system that includes all current policies, processes and procedures related to testing.

Question 3: Is it sufficient for the Laboratory Director/Designee to access the electronic learning management system to confirm that the traveling staff member has completed the appropriate training, and the competency assessment is current and successful?

CMS Response Q3:

“This issue is currently under discussion at CMS Baltimore. We will address all concerns and questions as quickly as we can. Thank you for your patience.”

Question 4: Is it sufficient, after confirmation of these activities, that the Laboratory Director document and approve this staff member to perform testing or must the traveling staff member have an additional competency assessment performed prior to testing in the other laboratory?

CMS Response Q4:

“The laboratory director establishes the written policies for competency assessment as outlined at the Code of Federal Regulations [42 CFR 493.1235](#). The competency assessment should be based upon the testing that’s performed in each laboratory.

Generally, there is one CLIA certificate for each laboratory location, and each laboratory is responsible for complying with the applicable CLIA requirements. If the staff members are working at locations that are all part of the same CLIA certificate (a multiple site situation)

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CMS Response Q4 (cont'd):

then the competency assessment documentation at the “home” facility should suffice. If the locations have different CLIA certificates, each location is responsible for performing and documenting its own competency assessment. The interpretive guidelines for the Code of Federal Regulations [42 CFR 493.1451\(b\)\(8\)](#) state that all testing personnel must be listed on the CMS 209 laboratory personnel report and must undergo documented competency assessment, using the six procedures denoted under the technical consultant or technical supervisor’s responsibilities for all testing performed. There should be documentation of competency assessment at each laboratory (i.e. for each CLIA certificate).

You can find additional information regarding the CLIA Competency Assessment requirements in the CLIA Competency Brochure, located on the CMS CLIA website.

https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/CLIA_CompBrochure_508.pdf”

Competency – Direct Observation

Background: Competency assessment requirements at [42 CFR 493.1413\(b\)\(8\)\(iv\)](#) and [42 CFR 1451\(b\)\(8\)\(iv\)](#) for moderate and high complexity laboratories include direct observation of performance of instrument maintenance and function checks.

In our example, weekly maintenance consists of cleaning the surfaces of the equipment or rinsing reagent and waste containers.

Question 5: Does competency assessment include direct observation of equipment cleaning?

Competency – Direct Observation (cont'd)

CMS Response Q5:

“Competency is the ability of personnel to apply their skill, knowledge, and experience to perform their laboratory duties correctly. Competency assessment is used to ensure that the laboratory personnel are fulfilling their duties as required by federal regulation.

The laboratory director establishes the written policies for competency assessment as outlined at the Code of Federal Regulations [42 CFR 493.1235](#). The competency assessment should be based upon the testing that’s performed in each laboratory.

The direct observations of employees are part of the competency assessment requirements for all personnel performing tests or procedures that are subject to CLIA as defined in the Code of Federal Regulations [42 CFR 493.1451\(b\)\(8\)](#).

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Competency – Direct Observation (cont'd)

CMS Response Q5 (cont'd):

The Laboratory Director is responsible for the overall operation and administration of the laboratory, including the employment of competent qualified personnel. See the Code of Federal Regulations [42 CFR 493.1445](#). Even though the Laboratory Director has the option to delegate some of her/his responsibilities, she/he remains ultimately responsible and must ensure that all the duties are properly performed and applicable CLIA regulations are met. It is the laboratory director's responsibility to define in policy and procedures personnel duties.”

Titers – anti-A and/or anti-B

Background: Donor centers are now performing anti-A and/or anti-B titers on donor samples to provide low-titer plasma, apheresis platelets, and group O whole blood, to hospitals.

Question 6: Do CLIA regulations apply to the testing used to determine these titers?

CMS Response Q6:

“The pre-donation tests (anti-A and/or anti-B titers) performed at donor centers are used to qualify the donor to donate products for the manufacture of blood products, which will be used to treat patients. Specifically, the testing that is performed on donor samples to confirm the donor has the titers necessary to qualify the product as low-titer plasma, low-titer apheresis platelets, and low-titer group O whole blood is intended to detect anti-A and/or anti-B antibodies. CMS considers the intended purpose of this test as an assessment

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Titers – anti-A and/or anti-B (cont'd)

CMS Response Q6 (cont'd):

an assessment of health of the donor, since the donor's reported test result is providing information of the donor's health status and that will determine whether or not the plasma from the donor can be donated and manufactured to treat patients. CLIA applicability is keyed to the definition of a "laboratory" in the CLIA regulations. The facilities conducting the testing in question qualify as laboratories under the CLIA definition and therefore, are subject to CLIA."

Remember to look for the Weekly Report article announcing that the transcript has been posted on our website:

[Ask the FDA and CLIA Transcripts](#)

*Thank
You!*

Contact AABB's Regulatory Affairs Staff at
regulatory@aabb.org