

WELCOME

Ask the FDA and CMS/CLIA

2023 AABB Annual Meeting

10/14/23

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)

Director, CT Programs and Global Outreach

- Faiqa Sadique, MS, SBB, MT(ASCP), CQA(ASQ)

If you have questions following this session, please contact us:

regulatory@aabb.org

Learning 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:

- Office of Blood Research and Review
 - **Anne Eder, MD PhD**, Acting Director
 - **Carlos Villa, MD PhD**, Associate Director of Special Projects
 - **Carmelita Bibby**, Consumer Safety Officer
- Office of Regulatory Affairs, Office of Biologic Products Operations
 - **Susan Turcovski**, Deputy Director
- Office of Therapeutic Products
 - **Hanh Khuu, MD**, Medical Officer

Our CMS Participants:

The following speakers 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

Look for:

 Association for the Advancement
of Blood & Biotherapies

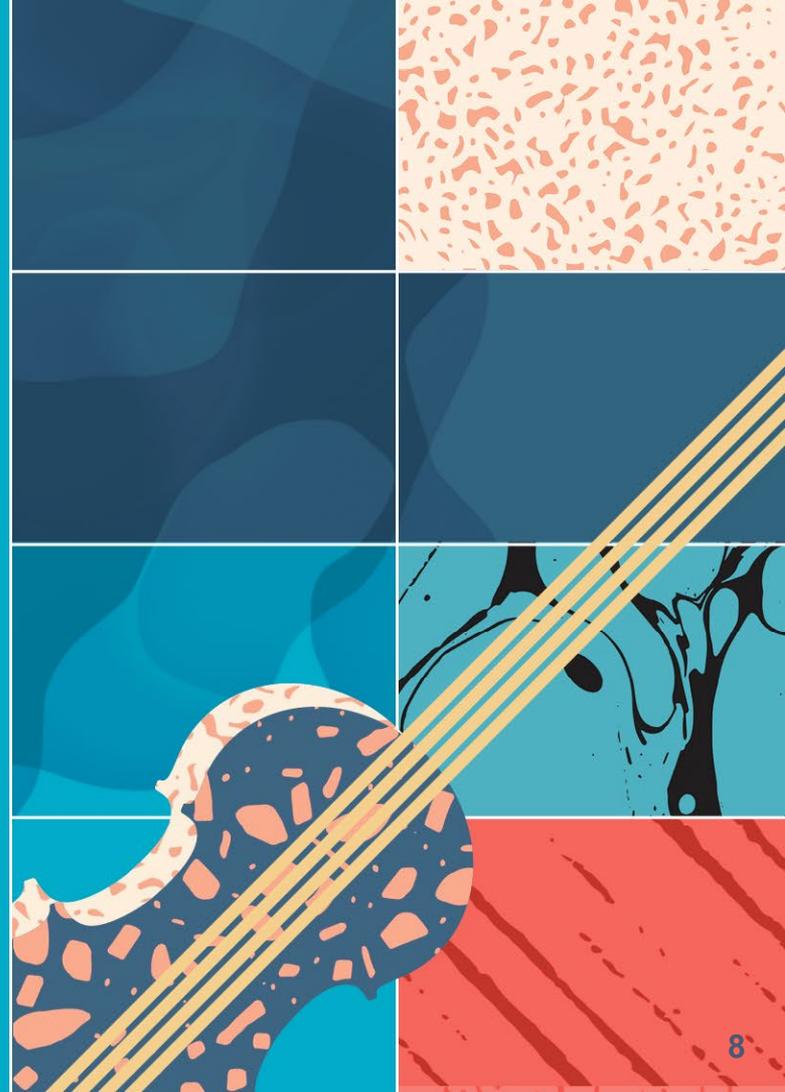
WeeklyReport

Sent to your INBOX every Wednesday!

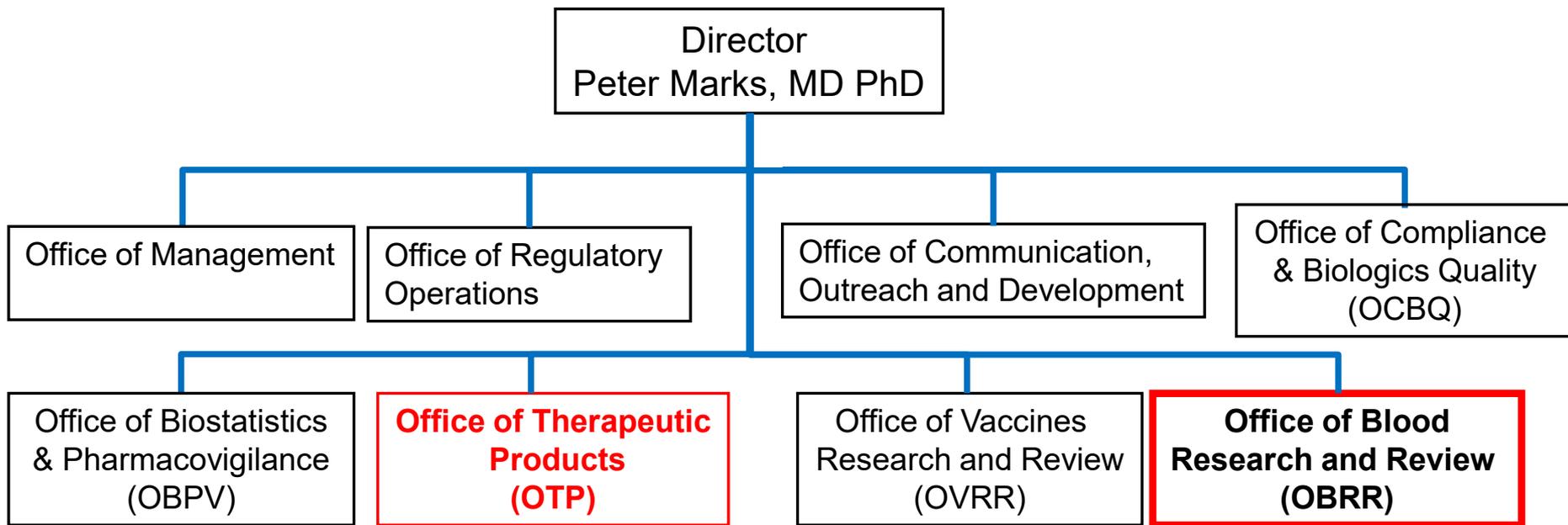
- Ask the FDA & CMS/CLIA Transcript
[Regulatory > Regulatory Resources > Ask The FDA and CLIA Transcripts](#)
- 2022-2023 Regulatory Updates Toolkit – a searchable PDF of all Regulatory articles from Weekly Report
- 2019-2022 Regulatory Updates

FDA Update

 **2023**
NASHVILLE
OCTOBER 14-17



Center for Biologics Evaluation and Research – Organization Chart



October 2023

Office of Blood Research and Review – HIV Individual Risk-Based assessment (IRA) Guidance and PrEP

- The May 2023 guidance on IRA to reduce the risk of HIV transmission by blood and blood products reflects FDA’s current recommendations on how to comply with 21 CFR 630.10(e) based on the available scientific data.
- 21 CFR 630.10(e) : “You must assess the donor’s medical history to identify risk factors closely associated with exposure to ...a relevant transfusion-transmitted disease (RTTI).” “A donor is ineligible to donate when information provided by the donor indicates possible exposure to an RTTI.”
- PrEP (e.g., Truvada) is indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV1 in adults at high risk.
- The available data demonstrate that the use of PrEP or PEP may delay the detection of HIV by currently licensed screening tests for blood donations, potentially resulting in false negative results in infected individuals.
- Because of the risk of false negative results, FDA recommends the deferral of donors on PrEP to ensure the safety, purity and potency of blood components.

Office of Blood Research and Review – Investigational COVID-19 Convalescent Plasma, Final Guidance, October 13, 2023

The expiration of the **COVID-19 public health emergency** under the Public Health Service Act on May 11 does not affect FDA's ability to authorize medical countermeasures for emergency use under section 564 of the FD&C Act. An **Emergency Use Authorization (EUA)** issued under section 564 of the FD&C Act (including for COVID-19 convalescent plasma) remains in effect for the duration of the relevant EUA declaration, unless FDA chooses to revoke the EUA because the criteria for issuance are no longer met, or revocation is appropriate to protect public health or safety.

Therefore, the emergency use of COVID-19 convalescent plasma remains in effect. The manufacture and use of CCP must be in accordance with the conditions described in the EUA.

(cont'd on the next page)

Office of Blood Research and Review – Investigational COVID-19 Convalescent Plasma, Final Guidance, October 13, 2023

- FDA issued guidance on October 13, 2023, which supersedes the guidance of the same title issued on Jan 7, 2022.
- **The recommendations in this guidance are unchanged from the January 7, 2022 guidance.**
- However, **we have removed the language that limited the duration of the policy in the guidance to the public health emergency related to COVID-19** declared by HHS in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act) (42 U.S.C.247d(a)(2)), which expired on May 11, 2023.
- **In preparation for when the EUA is no longer in effect**, blood establishments interested in submitting an IND or biologics license application for COVID-19 convalescent plasma may contact the Center for Biologics Evaluation and Research (CBER), Office of Blood Research and Review (OBRR).
- In addition, we intend to issue a guidance with recommendations for such submissions.

Office of Blood Research and Review: Prelicensure/Preapproval Inspection of New Facilities

Inspections of new Blood Center facilities:

- Effective November 1, 2023, CBER will lead inspections of new blood center facilities that have not been previously inspected by FDA.
- Inspection is required when facility has no inspectional history and firm submits a BLA supplement that requires site-specific approval:
 - Blood components (apheresis collections)
 - Manufacturing processes
- 15 inspections completed or scheduled since June 2023

Inspections of new Source Plasma facilities:

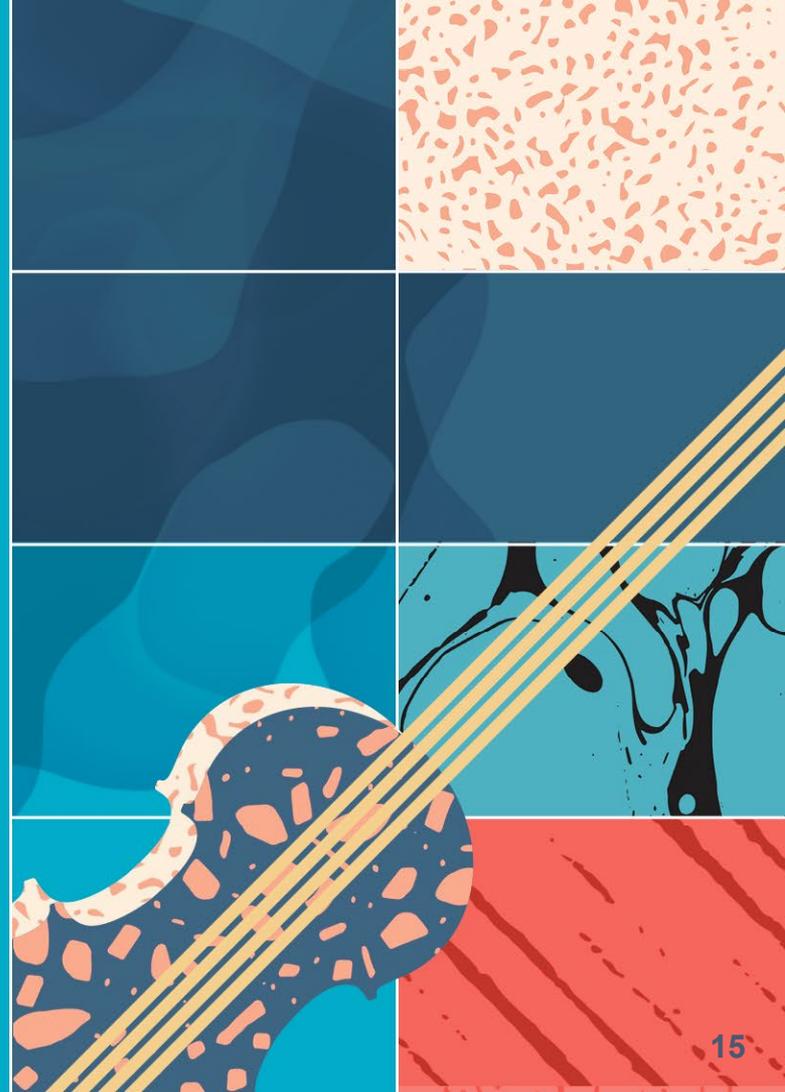
- CBER completed or scheduled 155 inspections since July 2022

Questions for Blood and Plasma Branch?

- Specific questions about changes to an approved application?
 - Contact the Regulatory Health Project Manager assigned to your submission
- General questions about blood regulations, recommendations in guidance, requirements?
 - Send to the Blood and Plasma Branch mailbox:
CBEROBRRBPBInquiries@fda.hhs.gov

ASK THE FDA

Blood and Blood Components



Container Label – Red Cell Volume

Background: [21 CFR 606.121](#) Container Label states:

“(c) The container label must include the following information, as well as other specialized information as required in this section for specific products:

(5) For Whole Blood, Plasma, Platelets, and partial units of Red Blood Cells, the volume of the product, accurate to within ± 10 percent; or optionally for Platelets, the volume or volume range within reasonable limits.”

[Circular of Information](#), December 2021, page 13 describes that:

“After plasma is removed, the resulting component is RBCs, which has a hematocrit between 65% to 80% and a usual volume between 225 mL and 350 mL” and “The typical hematocrit of AS RBCs is 55% to 65%, and the volume is approximately 300 to 400 mL.”

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Container Label – Red Cell Volume (cont'd)

In our example, a unit of RBCs is split and labeled as part A with a 100 mL volume and issued to a pediatric patient. The remainder of the unit contains 220 mL, is labeled as part B, and returned to storage. Close to the expiration date of part B, an order is received to transfuse one unit of RBCs to an adult patient.

Question 1: Is the 220 mL, part B unit of the split RBC an acceptable volume to fulfill an order to transfuse one unit of RBCs to an adult?

Question 2: Is there a minimum volume below which a split unit of RBCs is not an adequate dose for a “transfuse one unit of RBC” order on an average adult patient?



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Container Label – Red Cell Volume (cont'd)

FDA/OBRR Q1 and Q2:

“FDA does not have requirements for an acceptable minimum volume of RBC components to provide an adult dose of hemoglobin. The blood establishment’s Responsible Physician should determine the minimum volume of a unit of packed RBCs and a unit of RBCs suspended in additive solution that can be used as an acceptable dose of hemoglobin for an adult RBC transfusion.”



Container Label - Anticoagulant

Background: [21 CFR 606.121](#) Container label:

“(e)(1) Whole Blood labels must include:

(i) The name of the applicable anticoagulant approved for use by the Director, CBER.

(e)(2) Except for frozen, deglycerolized, or washed Red Blood Cell products, Red Blood Cell labels must include:

(i) The type of anticoagulant, and if applicable, the volume of Whole Blood and type of additive solution, with which the product was prepared.”

Question 3: [21 CFR 606.121\(e\)\(1\)](#) for Whole Blood requires labeling with the “name” of the applicable anticoagulant and [\(e\)\(2\)](#) requires labeling with the “type” of anticoagulant. What is the difference between these two labeling requirements?

(cont'd on the next page)

Container Label – Anticoagulant (cont'd)

FDA/OBRR Q3:

“The words, “Name” and “Type”, in these CFR references are used interchangeably. The "name" of the applicable anticoagulant described in 21 CFR 606.121(e)(1)(i) has the same meaning as the "type" of anticoagulant described in 21 CFR 606.121(e)(2)(i).”



Container Label – Paid Donor

Background: [21 CFR 606.121\(c\)\(8\)\(v\)\(B\)](#), defines: “A ‘volunteer donor’ is a person who does not receive monetary payment for a blood donation” and the 2019 [CPG Sec. 230.150 Blood Donor Classification Statement, Paid or Volunteer Donor](#) states, under section III. Policy, A. Paid Donors, page 2:

“Monetary payment includes cash, in any amount, and incentives that are readily convertible to cash.

...

D. Examples of Incentives 7, Page 6:

A gift card incentive is considered a monetary payment if readily convertible to cash. If a gift card is non-transferable, bears the donors name, and is not redeemable for cash, it would not be considered readily convertible to cash and blood and blood components collected should be labeled with the “volunteer donor” label statement.”

(cont'd on the next page)

Container Label – Paid Donor (cont'd)

This has been an ongoing topic in our collection center. We understand that when a donor receives monetary payment for a blood donation, all blood and blood components that are intended for transfusion must be labeled with the “paid donor” classification statement.

Question 4: Is it correct that any dollar value gift card, for example, a \$50 or \$100 VISA gift card may be given to a donor and the transfusable blood products collected may be labeled as from a “volunteer donor” as long as the gift card is not transferrable, bears the donor’s name, and is not redeemable for cash?

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Container Label – Paid Donor (cont'd)

FDA/OBRR Q4:

“According to the Compliance Program Guide CPG Sec. 230.150: Blood Donor Classification Statement, Paid or Volunteer Donor, if a gift card is nontransferable, bears the donor’s name, and is not redeemable for cash, it would not be considered readily convertible to cash and the blood and blood components intended for transfusion should be labeled with the “volunteer donor” label statement. The regulation and the relevant preambles are silent on whether the dollar value of the benefit is to be taken into account when determining whether a benefit is readily convertible to cash.”

(cont'd on the next page)

Container Label – Paid Donor (cont'd)

Question 5: Is it acceptable to limit the distribution of such gift cards only to donors who pass screening and are eligible to donate?

FDA/OBRR Q5:

“FDA does not have regulations or recommendations that address this question. If a center has specific questions around gift cards for voluntary donors, please contact us directly so that we can understand the specifics of your situation and not general examples.”

Container Label – CMV and Sickle Testing

Background: [21 CFR 606.121\(d\)](#) Container label requires:

“(d) Unless otherwise approved by the Director, CBER, the container label for blood and blood components intended for transfusion must be white and print must be solid black, with the following additional exceptions:

...

(2) The proper name of the product, with any appropriate modifiers and attributes, the donor classification statement, and the statement “properly identify intended recipient” may be printed in solid red or in solid black.”



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Container Label – CMV and Sickle Testing

(cont'd)

Our blood processing laboratory performs serologic testing for CMV, and solubility testing for hemoglobin S.

Question 6: Following testing, is it acceptable to place a colored sticker for attributes such as CMV negative or sickle cell negative on a blood component?

**CMV
NEGATIVE**

**SICKLE CELL
NEGATIVE**

(cont'd on the next page)

Container Label – CMV and Sickle Testing

(cont'd)

FDA/OBRR Q6:

“21 CFR 606.121(d) does not require or preclude the use of colored stickers to convey additional test results on blood component container labels. However, we recommend the ISBT 128 standard convention, using a special testing attribute code and text in the lower right quadrant of the container label.

For example, the code for “CMV seronegative” is N0008 and the code for “Hemoglobin S negative” is N0106.

Please refer to the ISBT128 website for the latest version, as recognized by the FDA in the June 2014 guidance for industry.”

Molecular Antigen Typing

Background: Our blood establishment has begun screening selected E, C, K antigen-negative donors for hemoglobin S using an FDA-approved molecular assay.

Question 7: Does the blood establishment have a responsibility to consent the donor to perform a hemoglobin S molecular assay or any type of sickle trait testing?

Question 8: Does the blood establishment have a responsibility to notify a donor of their sickle trait positive status when performed using an FDA-approved molecular assay?

Question 9: When hemoglobin S screening has been performed using an FDA-approved molecular assay, does the testing need to be repeated for each subsequent donation made by this donor or can an RBC component be labeled as sickle negative based off of historical testing?

(cont'd on the next page)

Molecular Antigen Typing (cont'd)

FDA/OBRR Q7 and Q8:

“FDA does not have specific requirements for consenting or notifying donors regarding testing for hemoglobin S. However, we recognize that there are donor health implications for sickle cell trait.

Consequently, FDA’s current thinking is that:

- Donors should be informed that their donations may be tested for hemoglobin S and that they will be notified of positive results
- Donors should be given the opportunity to decline testing or donation
- When hemoglobin S testing is performed after the blood center distributes the product, the transfusion services should inform the blood center in instances where a blood component is found to be positive for hemoglobin S.

(cont'd on the next page)

Molecular Antigen Typing (cont'd)

FDA/OBRR Q9:

“FDA does not have specific requirements or recommendations for testing donors or labeling units with historic hemoglobin S results. Blood establishments should develop procedures to determine how they will determine the hemoglobin S status of a donor based on results of historical testing and how they will label such testing.

Some points to consider:

- Some assays used to determine hemoglobin S status are screening tests and may not reflect the true hemoglobin S status of the donor. The type of assay used and whether it confirms the hemoglobin S status are factors that should be taken into consideration.
- Your Standard Operating Procedures (SOPs) should describe how you will perform and document hemoglobin S testing and maintain records of such tests.

(cont'd on the next page)

Molecular Antigen Typing (cont'd)

FDA/OBRR Q9 (cont'd):

- You should use a validated process to confirm the donor's identification and accurate linkage that relates the current donation to the hemoglobin S results from previous donations.
- You should convey to transfusion services your practices for labeling RBC units with historical hemoglobin S results.

Note that if blood establishments are manufacturing blood components with a device that includes instructions to test the component for HbS, the blood establishment must follow the manufacturer's instructions for use (21 CFR 606.65 (e)) and perform such testing accordingly."

Records – Cumulative Record



Background: Record Retention requirements, [21 CFR 606.160\(e\)\(2\)](#) require:

“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. In addition, establishments other than Source Plasma establishments must include in this cumulative record donors deferred from donation under [§ 610.41 of this chapter](#) because their donation tested reactive under [§ 610.40\(a\)\(2\) of this chapter](#) for evidence of infection due to HTLV or Chagas disease.”

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Records – Cumulative Record (cont'd)

Many blood collection facilities without the technology to electronically store very old deferral records pay a tremendous amount of money for secure off-site storage.

Question 10: Is the use of the term “cumulative” in [21 CFR 606.160\(e\)](#) intended to require an indefinite record retention requirement for old paper records of donors deferred from donation?



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Records – Cumulative Record (cont'd)

FDA/OBRR Q10:

“The specific CFR reference - 21 CFR 606.160(e)(2) - requires a cumulative record. It is not specific for digital or paper records. Your cumulative donor deferral record should be updated at least monthly to add new donors who are deferred due to relevant transfusion transmitted infections. Establishments must review the cumulative record to remove donors who have been requalified under 610.41(b).

Note that the cumulative record of deferred donors does not have a time limit, and blood establishments must keep records of donors deferred for evidence of relevant transfusion- transmitted infections indefinitely.”

Thermometer Calibration

Background: [21 CFR 606.60\(b\)](#) requires:

“Equipment that shall be observed, standardized, and calibrated with at least the following frequency, include but are not limited to:

Equipment	Performance check	Frequency	Frequency of calibration
Laboratory thermometers			Before initial use.
Electronic thermometers			Monthly.

An FDA-cleared water bath used to thaw plasma is equipped with a digital thermometer and used by the laboratory to monitor temperatures during the thawing cycle.

Question 11: Does this thermometer need to be calibrated monthly as an electronic thermometer?

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Thermometer Calibration (cont'd)

FDA/OBRR Q11:

“In accordance with 21 CFR 606.100(b)(10), your facility Standard Operating Procedures must include the instructions from the manufacturer’s Operator’s Manual for the frequency of observations and calibration of the thermometers. This approach will satisfy the requirement in 21 CFR 606.60(a) that “equipment shall be observed, standardized and calibrated on a regularly scheduled basis as prescribed in the Standard Operating Procedures Manual and shall perform in the manner for which it was designed so as to assure compliance with the official requirements prescribed in this chapter for blood and blood products.

The requirements in 21 CFR 606.60(b) for monthly calibration of electronic thermometers should be used only if the manufacturer’s Operators Manual/Instructions for Use for your system does not prescribe the frequency of calibration activities.”

Expiration Dating

Background: During the [2014 Ask the FDA session](#), FDA responded to the following question on expiration dating:

Question 30: *What should the product expiration date be if the ACDA solution used in the collection of Apheresis Platelets expires less than 5 days from the day of collection? Would you use the expiration date of solution or do the platelets expire as normal 5 days after collection?*

FDA's response: *The expiration date of the platelets would be based on the shortest expiration date of the supplies used and on the manufacturing process. So in this situation, the expiration date of the platelets would be based on the expiration date of the ACDA solution if there were no other manufacturing processing performed on the platelets that would thus impact the expiration date further.*

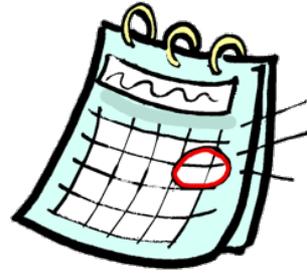
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Expiration Dating (cont'd)

Question 12: If the blood collection set/kit used for blood collection and manufacture of blood and blood components expires in 10 days, would the components manufactured (RBCs/FFP) using the collection set/kit expire in ten days?

FDA/OBRR Q12:

“The blood collection set/kit may be used up to the expiration date specified on the label, unless indicated otherwise in the manufacturer’s instructions for use. The expiration date in the example you provided applies to the collection set/kit, not the dating period for the blood components. The dating period for blood components is specified in 21 CFR 610.53, unless a different dating period is specified in the instructions for use of the blood collection, processing and storage system approved or cleared for such use by FDA.”



Use of Cold-Stored Platelets (CSPs)

Background: The June 2023 guidance, [Alternative Procedures for the Manufacture of Cold-Stored Platelets](#) was issued to respond to:

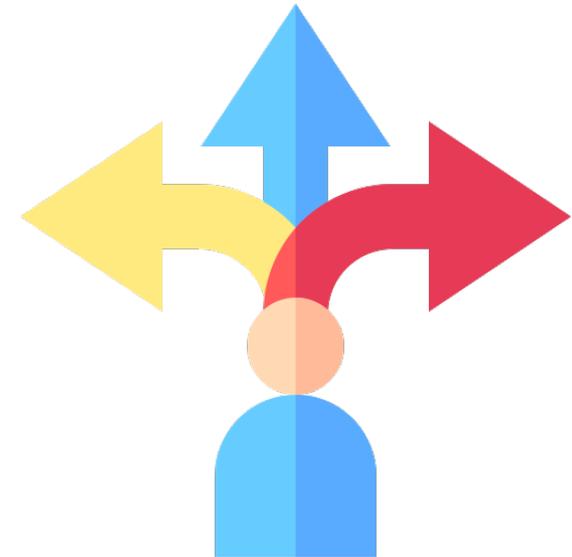
“a public health need to address the urgent and immediate need for platelets for the treatment of active bleeding when conventional platelets are not available, or their use is not practical. Maintaining platelet availability in the face of logistical challenges (e.g., in military, prehospital, or austere settings) or other threats to blood availability (e.g., mass casualty events or public health emergencies) is critical to assure that platelets are available to patients with active bleeding.”

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Use of Cold-Stored Platelets (CSPs) (cont'd)

We appreciate the flexibility provided in these recommendations and look forward to the agency's review of additional data which may expand their use in the future.

Question 13: For purposes of the current recommendations, is “...or their use is not *practical*” defined by each facility and the unique needs and location of their customers?



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Use of Cold-Stored Platelets (CSPs) (cont'd)

FDA/OBRR Q13:

“Thank you for the opportunity to clarify our recommendations in the June 2023 CSP guidance. In November 2019, considering increased interest from blood establishments, transfusion services, and other stakeholders, FDA held a Blood Products Advisory Committee meeting on the topic of cold stored platelets. During this meeting, presenters shared the available clinical and in vitro data on CSP with the committee and FDA, and those data are summarized in the background section of the June 2023 guidance. I encourage you to refer to the guidance background and BPAC meeting materials, available online, to find additional information.

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Use of Cold-Stored Platelets (CSPs) (cont'd)

FDA/OBRR Q13 (cont'd):

During the BPAC, FDA heard from presenters, the committee, and members of the public, regarding challenges in maintaining an available supply of platelets in certain scenarios such as military settings and rural hospitals where conventional platelets are not routinely kept in blood bank inventory. Considering the available data, and FDA's assessment of potential benefits and risks of CSP transfusion, FDA granted variances to certain blood establishments to manufacture CSP with a dating period of up to 14 days for use in such scenarios. Note that while the available data supported use of CSP in certain scenarios, the committee and FDA also recognized the need for additional data to support the use of CSP where conventional platelets are an available alternative, and to inform appropriate dating periods. Trials examining this are underway. Until such data are available, FDA's thinking is that, when platelets are indicated for an actively bleeding patients, it is appropriate to use a conventional (in other words, room temperature stored) platelet product first.

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Use of Cold-Stored Platelets (CSPs) (cont'd)

FDA/OBRR Q13 (cont'd):

Considering FDA's assessment of individual variance requests to manufacture CSP, we determined that it was appropriate to grant a variance to blood establishments under 21 CFR 640.120(b), to assure the availability of platelets to treat active bleeding when conventional platelets are not available, or their use is 10/10/23 not practical. Examples of our current thinking on where the use of conventional platelets would not be practical include:

- Scenarios where platelet agitation cannot be reliably maintained (for example, prehospital emergency medical services)
- Scenarios where a conventional platelet supply cannot be reliably maintained due to infrequent use that would result in unacceptable rates of outdate (for example, some rural hospitals)
- During certain emergencies that threaten platelet availability (for example, mass casualty events)

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Use of Cold-Stored Platelets (CSPs) (cont'd)

FDA/OBRR Q13 (cont'd):

We recognize that certain scenarios may require blood establishments and transfusion services to assess the needs and locations of their customers to determine if it is appropriate to manufacture, distribute, and/or use CSP consistent with the recommendations in the guidance. In the following questions from the AABB community, we will run through examples of different scenarios and provide our assessment.”

Use of CSPs

Background: In these example scenarios, a large blood collector supplies the needs of urban trauma centers, oncology centers, and rural hospitals.

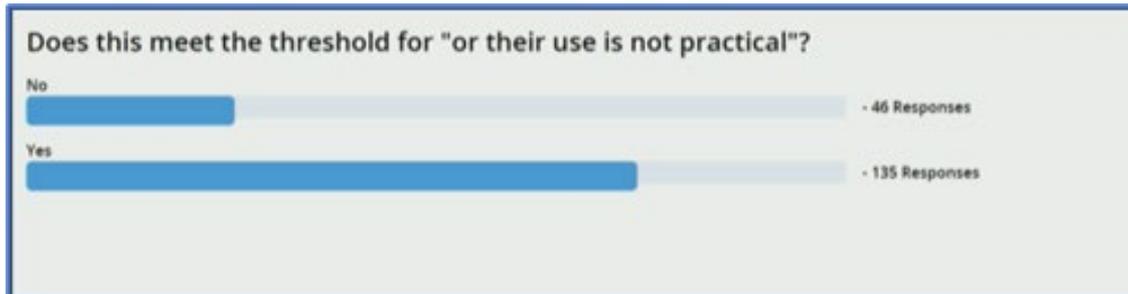
Scenario 1: The blood collector routinely has a supply of both room-temperature platelets (RTP) and cold-stored platelets (CSP) in its inventory. A decision is made to supply the rural hospital, which is located 3 hours away and does not provide oncology care, with CSP to treat actively bleeding patients arriving in their emergency room or actively bleeding during surgery. The large blood collector has determined that even though RTPs are available at the time of shipment, supplying this rural hospital with RTPs “is not practical” as CSPs provide an extended outdate and do not require bacterial risk control strategies. If a “non-actively bleeding patient” were to need platelets, an RTP would be shipped to meet this need.

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Use of CSPs (cont'd)

FOR AUDIENCE RESPONSE: Options (1) No (2) Yes

Question 14: Does this meet the threshold for “or their use is not practical?”



Use of CSPs (cont'd)

FDA/OBRR Q14:

“Yes. Based on the description, our understanding is that the rural hospital does not routinely maintain conventional platelets in their transfusion service inventory because their use would not be practical.”

Use of CSPs (cont'd)

Scenario 2: The large urban trauma center supplied by the collection facility has decided to stock both RTPs and CSPs. The CSPs will be used in the emergency room for actively bleeding trauma patients. This allows the RTPs to be available for their large oncology service.

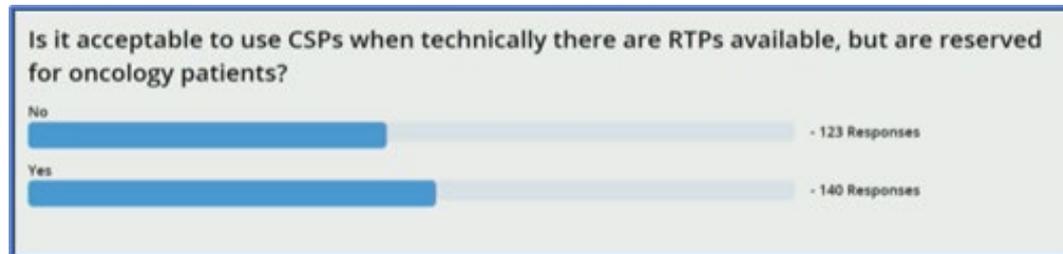


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Use of CSPs (cont'd)

FOR AUDIENCE RESPONSE: Options (1) No (2) Yes

Question 15: Is it acceptable to use CSPs when technically there are RTPs available, but are reserved for oncology patients?



Use of CSPs (cont'd)

FDA/OBRR Q15:

“No. Based on the description, the transfusion service routinely maintains a supply of conventional platelets, which are available, and these should be the first option when platelet transfusion is indicated for actively bleeding trauma patients. The description in this scenario is considered routine inventory management, which is not consistent with the recommendations in the guidance. If the transfusion service were to keep a supply of CSP for use in actively bleeding patients when conventional platelets are not available, that would be consistent with the guidance.”

CSP – Validation and Quality Control

Background: The 2007 *Guidance*, [Collection of Platelets by Automated Methods](#), page 11 describes a validation plan for pH using a

“...statistically sound sample size, based on 95% confidence that 95% of components (pH)...will meet the recommended results.”

The June 2023 *Guidance*, [Alternative Procedures for the Manufacture of Cold-Stored Platelets](#) provides a process validation approach consistent with a

“...CSP manufacturing process using a binomial distribution statistical sampling plan to demonstrate with 95% confidence that greater than 75% of the platelets stored at 1-6 C maintain a pH not less than 6.2 at the end of storage.”

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CSP – Validation and Quality Control (cont'd)

The two guidance documents provide examples of binomial sampling plan statistical approaches with differing criterion, the 2007 with 95/95 criterion and the 2023 with 95/75 criterion.

The [2023 CSP Guidance](#), Quality Control Testing, page 8 states:

“Blood establishments must conduct monthly pH quality control (QC) testing on CSP, and that testing must be performed in accordance with the QC statistical sampling plan as described in the firm’s written procedures (21 CFR 640.25 (b)(2), 21 CFR 211.160(b), and 21 CFR 211.165(c)). The number of CSP components included in the overall monthly QC testing plan should represent the proportion of CSP in the total platelet inventory. For example, if 20% of your total platelet inventory is CSP, you should include that proportion of CSP in your monthly QC platelet testing plan.”

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CSP – Validation and Quality Control (cont'd)

Question 16: With the RTP *Guidance* referencing a 95/95 validation sampling plan and the [2023 CSP Guidance](#) referencing a 95/75 validation sampling plan, it is difficult to determine the sample size for an overall monthly QC testing plan. Should we set our sample size for pH based on 95/95 or 95/75?



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CSP – Validation and Quality Control (cont'd)

FDA/OBRR Q16:

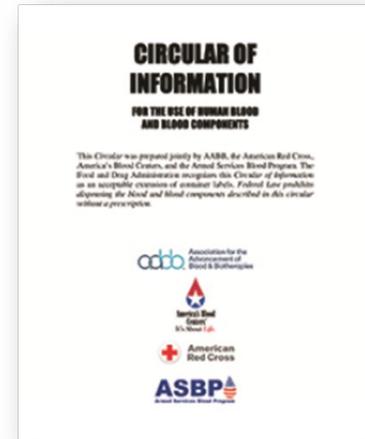
“The recommendation in the CSP guidance for a 95%/75% pH statistical sampling plan is for process validation for manufacturing of CSP only. We considered that we could reduce the testing burden for process validation of CSP, because most establishments already have a validated process for manufacturing room temperature conventional apheresis platelets.

This is different from the recommendation for monthly pH QC testing, which has not changed and is a 95%/95% statistical sampling plan for monthly pH QC testing that should include both CSP and room temperature platelets. In accordance with the CSP guidance, blood establishments must include CSP in their monthly pH Quality Control (QC) testing, and that testing must be performed in accordance with their QC statistical sampling plan as described in their written procedures. The CSP monthly pH QC data should be incorporated into their current overall monthly QC statistical sampling plan for platelets, proportional to the percentage of CSP collected.”

Circular of Information - CSP

Background: We are a hospital-based blood collection center and we *do not manufacture* cold-stored platelets; therefore, our [December 2021 Circular of Information](#) does not contain the additional FDA required language for CSPs provided on the [AABB's Circular page](#). However, we do purchase CSPs from an outside supplier. Their *Circular* does include the additional language for CSP added to the first two pages designated for this purpose.

Question 17: Should we add this information to the front of our *Circular* when we distribute CSPs to our Transfusion Service?

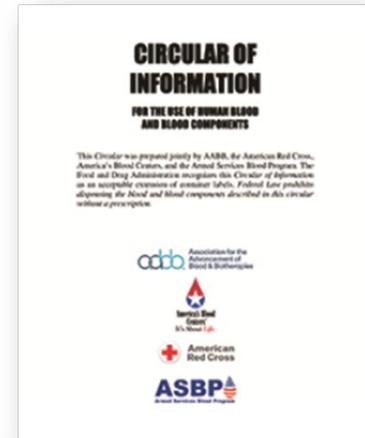


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Circular of Information – CSP (cont'd)

FDA/OBRR Q17:

“If you are purchasing CSP from an outside supplier, the supplier must provide their Circular of Information that contains adequate directions for the use of CSP. We recommend that you request your CSP supplier provide you with copies of their revised COI with this language.”



Circular of Information – Cryoprecipitated AHF

Background: [21 CFR 640.56](#) U.S. Quality control test for potency provides the following requirements:

“(a) Quality control tests for potency of antihemophilic factor shall be conducted each month on at least four representative containers of Cryoprecipitated AHF.

...

(d) If the average potency level of antihemophilic factor in the containers tested is less than 80 units of antihemophilic factor per container, immediate corrective actions shall be taken and a record maintained of such action.”

and

(cont'd on the next page)

Circular of Information – Cryoprecipitated AHF (cont'd)

[21 CFR 606.122](#) *Circular of Information* includes the following language:

“A circular of information must be available for distribution if the product is intended for transfusion. The circular of information must provide adequate directions for use, including the following information:

(n) For Cryoprecipitated AHF, the circular of information must contain:

- (1) A statement that the average potency is 80 or more International Units of antihemophilic factor.*
- (2) The statement: ‘Usually contains at least 150 milligrams of fibrinogen’; or, alternatively, the average fibrinogen level determined by assay of representative units.”*

(cont'd on the next page)

Circular of Information – Cryoprecipitated AHF (cont'd)

Fibrinogen testing is not required in [21 CFR 640.56](#) quality control test for potency, but a labeling statement on fibrinogen content is required in the *Circular*.

Question 18: Does FDA require monthly quality control testing of fibrinogen concentration in cryoprecipitated AHF to support this labeling statement?

FDA/OBRR Q18:

“To comply with the requirements for acceptable fibrinogen levels as stated in 21 CFR 606.122(n)(2), we expect blood establishments to include fibrinogen testing as part of their quality control testing. We are aware that blood establishments test for fibrinogen while performing monthly testing for Factor VIII.”

Leukocyte Reduction

Background: Despite near unanimous votes of three separate advisory committees over the last 20+ years, FDA has not recommended universal leukocyte reduction of cellular blood transfusions:

[Blood Products Advisory Committee](#) September 1998

[Advisory Committee to HHS on Blood Safety and Availability](#) January 2001

[Transmissible Spongiform Encephalopathies Advisory Committee](#) June 1, 2015

Since those advisory committee meetings, additional evidence has been published that removing white cells, histones, neutrophil extracellular traps, and DNA by pre-storage leukoreduction may reduce TRALI and TACO and this possibility is supported by animal model studies showing that histones are a potential major cause of lung injury.

(cont'd on the next page)

Leukocyte Reduction (cont'd)

Infusing red cells that are not leukocyte-reduced increases transfusion reactions, HLA and red cell alloimmunization, platelet refractoriness and post-operative infections. These adverse effects are seen in populations receiving selectively leukocyte-reduced transfusions because we often do not know the correct diagnosis at the time of transfusion (e.g., myelodysplastic syndrome vs. simple anemia). In cardiac surgery patients, leukoreduction reduces mortality by 50% in randomized trials.

The evidence that leukoreduction reduces patient morbidity, and mortality in many clinical settings is overwhelming and the cost is modest.

Question 19: Will FDA be considering a recommendation or regulation for universal leucocyte reduction sometime in the near future?

(cont'd on the next page)

Leukocyte Reduction (cont'd)

FDA/OBRR Q19:

“There are no current FDA recommendations or requirements for universal leukoreduction. FDA recognizes the benefits of leukoreduction of blood components and encourages its use. Based on the most recent National Blood Collection and Utilization Survey, we also recognize that industry has achieved high rates of leukoreduction practices.

We note that FDA’s guidance and rulemaking plans are of great interest to a wide range of stakeholders. CBER publishes an annual guidance agenda to inform stakeholders of the guidance topics CBER is considering for development in the coming year. Further, a listing of upcoming FDA rulemakings is included in the Federal Government’s Unified Agenda of Regulations that is published in the Federal Register, usually in the Spring and fall. These mechanisms allow for all stakeholders to be informed about FDA’s future policy and regulatory agendas.”

May 2023 HIV Guidance – PrEP & PEP

Background: Regarding the May 2023 FDA “[Recommendations for Evaluating Donor Eligibility Using Individual Risk-Based Questions to Reduce the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products](#),” III. B. Donor Deferral recommendations, page 8:

3. *“Defer for 3 months from the most recent dose, an individual who has taken any medication by mouth (oral) to prevent HIV infection (i.e., antiviral PrEP or PEP).”*
4. *“Defer for two years from the most recent injection, an individual who has received any medication by injection to prevent HIV infection (e.g., longacting antiviral PrEP or PEP).”*

(cont'd on the next page)

May 2023 HIV Guidance – PrEP & PEP (cont'd)

Question 20: Would the agency allow for exceptions to the 3-month and 2-year deferral for donors taking oral or injected medications (to prevent HIV infection) for blood products collected that are viral inactivated or further manufactured?

FDA/OBRR Q20:

“No. The HIV guidance reflects FDA’s current recommendations based on available scientific data. Consequently, we do not intend to allow exceptions to the 3-month and 2-year deferral for donors taking oral or injected medications to prevent HIV infection for blood products collected that are viral-inactivated or for further manufacture.”



Source Plasma

Background: During 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 21: 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?

(cont'd on the next page)

Source Plasma (cont'd)

FDA/ORA Q21:

“An affidavit is a statement of facts and are used in FDA for a variety of reasons. For example, in FDA, affidavits are generally used to document movement in interstate commerce of a FDA regulated product or component used to manufacture a product and in connection with the collection of samples. Affidavits may also be used for taking statements on consumer complaints, to document information obtained from informants, and to document voluntary destructions of violative products. For inspections conducted by ORA, affidavits may be used to document statements from anyone who has dealt with biologic products handled at the facility, to include raw materials, components and equipment, e.g. blood collection bags, and to document jurisdiction. The statement of facts in an affidavit are from persons who have dealt with the FDA regulated product and know material facts related to the manufacture of the product and/or to events affecting their condition. Although an FDA investigator develops the affidavit based on the facts that were provided to him/her, the affidavit is presented to the firm representative for review of the facts and their signature as the affiant.

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Source Plasma (cont'd)

FDA/ORA Q21 (cont'd):

It is not a routine practice to present affidavits during our inspections of Source Plasma or blood establishment facilities. ORA's Office of Biological Products Operations is aware of those few instances where an affidavit was presented during inspections when a newer investigator was being trained and/or audited. The use of affidavits is outlined in the Investigations Operations Manual which is publicly available on FDA's website."

Changes to an Approved Application – Blood Establishment Computer System

Background: The Dec 2014 Guidance, [Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture](#), Appendix D: shows the following:

Contains Nonbinding Recommendations

APPENDIX D: REPORTING CHANGES ASSOCIATED WITH BLOOD ESTABLISHMENT COMPUTER SOFTWARE (BECS)

Type of Change	Reporting Category			
	PAS	CBE30	CBE	AR
Other BECS Applications				
A. Initial implementation of 510(k) cleared BECS that interfaces with an apheresis device to permit bi-directional data flow impacting the operation of the apheresis device with regard to (not an all-inclusive list) sending eligible product combinations, donor information, and initial configuration information to the apheresis device and determining component eligibility based on the interval, frequency, non-rinse back events and RBC/Plasma loss from a donor's past donations.		X		
B. Implementation of a blood establishment computer system that is interfaced with an automated blood cell separator device as described in the 510(k) clearance for the software.	X			

(cont'd on the next page)

Changes to an Approved Application – Blood Establishment Computer System (cont'd)

Question 22: Line A and Line B in **Appendix D** indicate a CBE30 or PAS is needed for what seems like the same scenario. Can clarification be provided regarding the difference between the line items?



(cont'd on the next page)

Changes to an Approved Application – Blood Establishment Computer System (cont'd)

FDA/OBRR Q22:

“The scenarios in the guidance document are intended to indicate different circumstances based on the specific clearance and intended use of the devices. Blood establishments with questions about the appropriate reporting category based on their specific circumstances should contact OBRR directly. You can use the OBRR inquiry email box at CBEROBRBPBInquiries@fda.hhs.gov.”

HIV Lookback and Pathogen Reduction

Background: [21 CFR 610.46](#) provides the HIV “lookback” requirements for consignee notification. I have a question regarding consignee notification of reactive infectious disease testing. A platelet donor was recently HIV reactive (negative confirmation test) for a donation. We are in the process of performing our lookback. Some of the previous donations from this donor in the lookback window are pathogen-reduced platelets that were shipped out to other facilities.

Question 23: Are we required to notify these receiving facilities in writing for pathogen-reduced products?



(cont'd on the next page)

HIV Lookback and Pathogen Reduction

(cont'd)

FDA/OBRR Q23:

“If a donor has reactive test results for HIV and you initiate the lookback process, you must follow all the requirements as described in 21 CFR 610.46 including consignee notification in writing. The regulation applies to all blood components, including pathogen reduced products.”

Syphilis - Further Testing after a Reactive Screening Test

Background: For donor screening for Syphilis, our lab uses an FDA-cleared non-treponemal test for the initial screening test. If this test result is reactive, the lab initiates a subsequent test using a treponemal test that is not cleared as a supplemental test but is a diagnostic test.

The [December 2020 Syphilis guidance](#), Section IV.B., page 6, is very clear that the serological screening test for syphilis must be cleared by FDA for such use but does not mention clearance for the diagnostic test.

Question 24: Does this diagnostic treponemal test need to be FDA cleared as a diagnostic test for use in further testing?



(cont'd on the next page)

Syphilis - Further Testing after a Reactive Screening Test (cont'd)

FDA/OBRR Q24:

“Yes, if you use a diagnostic test for syphilis to meet the requirement for further testing in 610.40 (e), it must be FDA-cleared, approved or licensed.

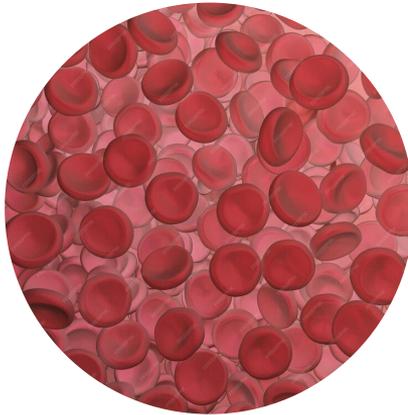
The Syphilis guidance states that if the non-treponemal test screening test is reactive, you must perform further testing as required in 21 CFR 610.40(e).

This regulation requires that the test used for further testing must be licensed, approved, or cleared, as follows (21 CFR 610.40(e):

“You must further test each donation, including autologous donations, found to be reactive by a donor screening test ... using a licensed, approved, or cleared supplemental test, when available. If no such supplemental test is available, you must perform one or more licensed, approved, or cleared tests as adequate and appropriate to provide additional information concerning the reactive donor’s infection status.”

Hereditary Hemochromatosis and Blood Donation

Background: I have hereditary hemochromatosis which requires therapeutic phlebotomy. I am otherwise healthy and thought that I could donate blood for others because there is nothing wrong with my blood. But I was told by the blood center when I tried to donate blood that FDA prohibits blood donation by individuals with hereditary hemochromatosis.



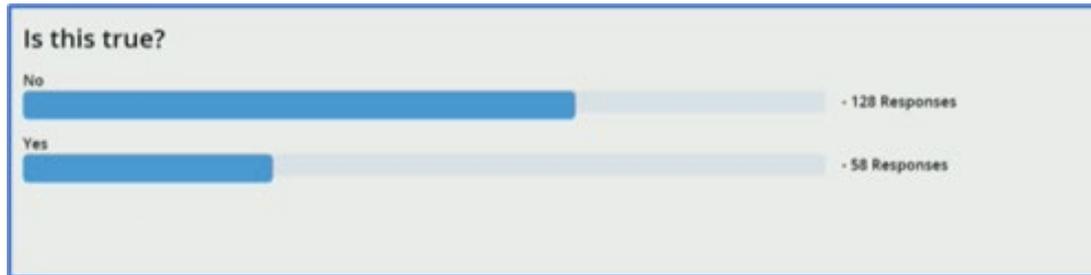
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Hereditary Hemochromatosis and Blood Donation

(cont'd)

FOR AUDIENCE RESPONSE: Options: (1) No (2) Yes

Question 25: Is this true?



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Hereditary Hemochromatosis and Blood Donation

(cont'd)

FDA/OBRR Q25:

“No. FDA does not prohibit blood donation by individuals with hereditary hemochromatosis.

If an individual with hereditary hemochromatosis requires therapeutic phlebotomy under a healthcare provider’s prescription and requires more frequent phlebotomy to treat their condition, there are specific regulations that govern the practice to use blood collected during a therapeutic phlebotomy for transfusion to others, under 21 CFR 630.15 (b)(2).”

Routine donation does not require a prescription from a healthcare provider and cannot be more frequent than allowed by regulation under 21 CFR 630.15 (a), which states that an individual must not donate a single unit of Whole Blood or Red Blood Cells by apheresis more than once in 8 weeks, or two units of Red Blood Cells by apheresis more than once in 16 weeks.”

Secondary Polycythemia and Therapeutic Phlebotomy

Background: Individuals undergo therapeutic phlebotomy for a number of reasons including primary and secondary polycythemia.

Question 26: What are the regulations and/or guidance documents that refer to donor eligibility requirements especially regarding patients with secondary polycythemia undergoing therapeutic phlebotomy?

Question 27: Does a diagnosis of polycythemia-vera (primary polycythemia) make a person ineligible to donate blood for life?



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Secondary Polycythemia and Therapeutic Phlebotomy

(cont'd)

FDA/OBRR Q26:

“Secondary polycythemia may be an appropriate physiologic response, for example to high altitudes or smoking, or reflect an underlying condition, such as COPD or kidney disease, as opposed to primary polycythemia due to a 10/10/23 hematologic malignancy. Please note that there is a distinction between a routine blood donation by a healthy individual and a therapeutic phlebotomy that is necessary treatment for a medical condition.

FDA’s regulations permit routine blood donations from individuals with secondary polycythemia provided they meet all donor eligibility requirements described in 21 CFR 630.10 and 21 CFR 630.15. Routine donation does not require a prescription from a healthcare provider and cannot be more frequent than allowed by regulation under 21 CFR 630.15 (a), which states that an individual must not donate a single unit of Whole Blood or Red Blood Cells by apheresis more than once in 8 weeks, or two units of Red Blood Cells by apheresis more than once in 16 weeks.

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Secondary Polycythemia and Therapeutic Phlebotomy

(cont'd)

FDA/OBRR Q26 (cont'd):

If an individual with secondary polycythemia requires therapeutic phlebotomy under a healthcare provider's prescription and requires more frequent phlebotomy to treat their condition, there are specific regulations that govern the practice to use blood collected during a therapeutic phlebotomy for transfusion to others, under 21 CFR 630.15 (b)(2)(iii). For diseases or conditions other than hereditary hemochromatosis, such as secondary polycythemia, you must determine that the health of a donor with that disease or condition will not be adversely 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.”

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Secondary Polycythemia and Therapeutic Phlebotomy

(cont'd)

FDA/OBRR Q26 (cont'd):

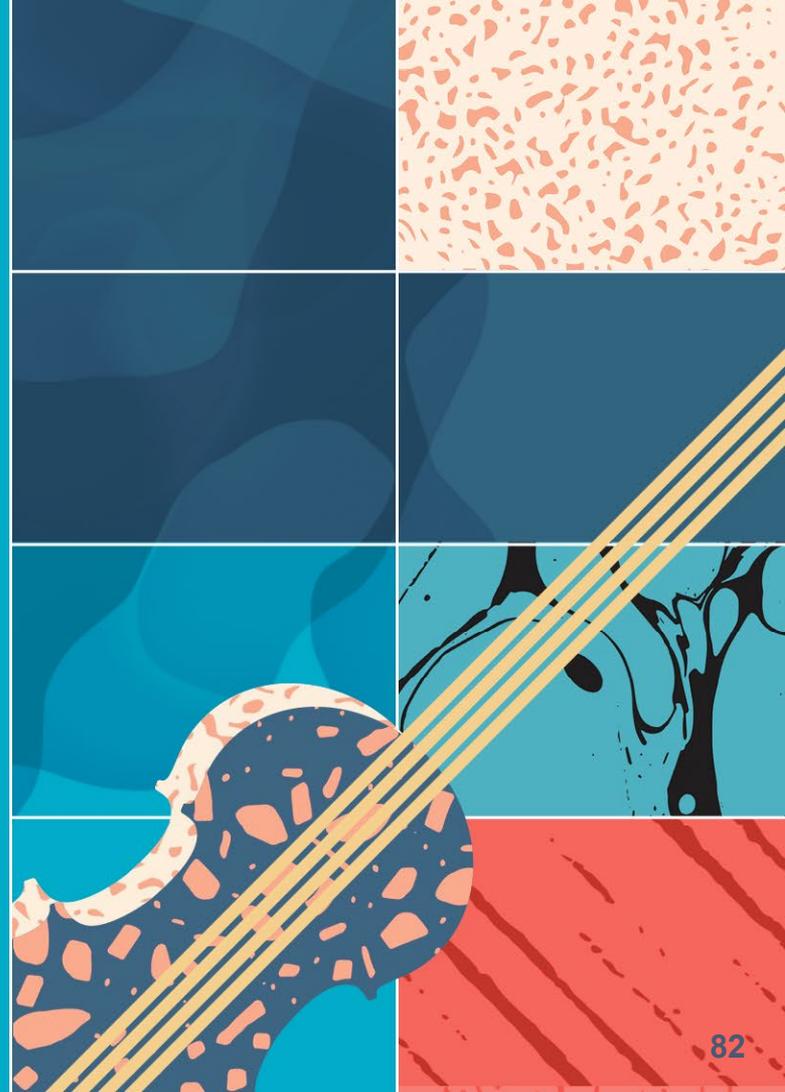
“If you intend to use blood collected from individuals with secondary polycythemia during therapeutic phlebotomy, you must submit your standard operating procedures to FDA for review. If you are a licensed blood center, you should submit a Prior Approval Supplement (PAS).”

FDA/OBRR Q27:

“Evaluation of a donor’s eligibility to donate blood includes several questions about different medical conditions, such as cancer. 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)). Polycythemia vera is a hematologic malignancy. FDA is aware that the practice in blood centers is to defer donors with this condition permanently.”

ASK THE FDA

Cellular Therapy



Flow Cytometers



Background: We are planning for an IND submission for our HCT/P product regulated under section 351 of Public Health Services Act (PHA) and are in the process of obtaining an instrument (such as a flow cytometer) for testing of this product under IND during the manufacturing process.

Question 1: Can a medical device such as flow cytometer that is not FDA approved/cleared be used for testing or processing a product under an IND, without first obtaining such an approval/clearance for the testing device (flow cytometer) from FDA?

Question 2: If permissible, what disclaimer if any would be required on the test report?

(cont'd on the next page)

Flow Cytometers



FDA/OTP Q1 and Q2:

“Yes, the flow cytometer that is not FDA cleared as a medical device can be used as an instrument for product testing as part of the manufacturing process under an IND. A test report should contain sufficient information to understand the suitability of the methods used with the instrument to include but not limited to sample preparation, gating strategy and the summary of data analysis and results with specifications.”

Question 3: Does FDA have plans to finalize the [Proposed Rule](#) for the exemption of certain flow cytometers from the 510k clearance process?

FDA/OTP Q3:

“Since we are CBER, we recommend that you reach out to the contact information listed at the Center for Devices and Radiological Health, CDRH on the proposed plans.”

Importing Products into the US – WNV Testing

Background: FDA’s 2016 Guidance, “[Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Living Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products \(HCT/Ps\)](#)” outlines FDA’s recommendations for WNV testing in Section III. Recommendations, A. 1 and 2, page 9:

“A. Living HCT/P donors should be tested for WNV using an FDA-licensed NAT donor screening test.^{3,4}

1. For establishments located within the United States (includes the 50 states and District of Columbia), we recommend performing WNV testing on HCT/Ps recovered from June 1st through October 31st every year.

...

(cont’d on the next page)

Importing Products into the US – WNV Testing (cont'd)

...

2. For all other establishments not specified above, and intending to import HCT/Ps into the United States, testing of HCT/P donors for WNV should be performed year-round.”

Our HCT/P manufacturing facility, located outside of the US, is planning on exporting cellular therapy products into the US. Our competent authority has determined that the prevalence of WNV in our country is low to nonexistent and therefore has not recommended testing but does require screening of donors for signs and symptoms of infection and exposure because of travel to endemic regions and deferral from donation for a period of 120 days.

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Importing Products into the US – WNV Testing (cont'd)

Question 4: Do FDA requirements for WNV testing of HCT/P donors still apply when exporting products into the US, even though our competent authority does not require such testing?

FDA/OTP Q4:

“We refer you to the FDA website title Importing CBER Regulated Products into the United States. In order to import a CBER regulated product into the United States the product must meet FDA regulatory requirements. This web page also contains other helpful information for establishments that plan to import CBER regulated products into the U.S. Therefore, establishments intending to import HCT/P's into the U.S. should refer to regulation under 21 CFR part 1271 and guidance documents for HCTP's including but not limited to the 2016 West Nile Guidance described in your question.”



Importing Products into the US – WNV Testing (cont'd)

Question 5: If the requirements do still apply, is it acceptable to export our HCT/P products without WNV testing, if the label states: “Not tested for WNV” and we provide a donor sample for testing to the US facility so they can perform the necessary testing before administration of the product?

FDA/OTP Q5:

“As we mentioned earlier, in order to import a CBER regulated product into the U.S. the product must meet FDA's regulatory requirements. Manufacturers, clinical investigators, and other members of regulated industry can submit their questions to industry.biologics@fda.hhs.gov.”

Harmonization of CGT Regulations

Background: Many cellular and gene therapy (CGT) products under development are manufactured with the intent to be distributed globally, however, global regulations vary from region to region and can make it difficult to ensure a product meets requirements to be distributed to the US.

Question 6: When developing new CGT guidance and regulations, does FDA consider what other peer regulatory agencies have provided on the topic?

FDA/OTP Q6:

“FDA often discusses guidance under development with peer regulatory agencies for commenting purposes. Regulations are not discussed outside of the FDA.”

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Harmonization of CGT Regulations (cont'd)

Question 7: Is there an intent to harmonize CGT regulations globally?

FDA/OTP Q7:

“Collaborations with global regulatory authorities are a priority for FDA. FDA often consults with other regulators when developing guidance for cell and gene therapy products.

In an environment where regulations differ, and harmonization of regulations is not feasible, global regulatory approaches for CGT are focused on convergence. Convergence is a process whereby regulatory approaches become aligned through common or similar practices and procedures that align with shared principles, or adoption of regulatory mechanisms to achieve the common goal of increasing the availability of safe and effective CGT products.”

HCT/P Donor Deferral Recommendations for PrEP or PEP

Background: The FDA [May 2023 HIV Guidance](#) for blood and blood components, Section III, Recommendations, B. Donor Deferral, page 8, recommends the following blood donor deferral periods:

3. *“Defer for 3 months from the most recent dose, an individual who has taken any medication by mouth (oral) to prevent HIV infection (i.e., antiviral PrEP or PEP).*
4. *Defer for two years from the most recent injection, an individual who has received any medication by injection to prevent HIV infection (e.g., longacting antiviral PrEP or PEP).”*

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HCT/P Donor Deferral Recommendations for PrEP or PEP

HCT/P donor blood samples are tested for infectious disease testing in the same manner as blood donors using FDA-approved tests.

Question 8: What are FDA's recommendations for a deferral period for HCT/P donors who may be taking the same antiretroviral medications?



HCT/P Donor Deferral Recommendations for PrEP or PEP

FDA/OTP Q8:

“I want to thank OBRR for bringing up the topic. For the purpose of determining eligibility for donors of HCT/P's, you must comply with regulations in 21 CFR part 1271 and should continue to use the guidance documents related to HCT/P's including but not limited to the 2007 Guidance titled Eligibility Determination for Donors of Human Cells, Tissues and Cellular and Tissue-Based Products. FDA tissue guidance website has all the guidance documents related to HCT/P donor eligibility which includes screening donors to reduce the risk of transmission of HIV. We also refer you to FDA's website titled Guidance Agenda, guidance documents CBER is planning to publish during the calendar year 2023 that was brought up and discussed by my CBER colleagues. You will note that the guidance title recommendations for determining eligibility of donors of HCT/Ps is being considered for publication in 2023. As explained on this website, CBER is neither bound

(cont'd on the next page)

HCT/P Donor Deferral Recommendations for PrEP or PEP

FDA/OTP Q8 (cont'd):

this list of topics, nor required to issue every guidance on the list. The agency is also not precluded from developing guidance documents on topics that are not on the list. Should there be any changes to HCT/P donor screening or testing recommendations they will be communicated to industry through guidance. One last point, the guidance documents related to screening and testing of blood donors are not applicable to donors and HCT/P's. If you have direct questions, we invite you to write to us at industry.biologics@fda.hhs.gov.”

Minimally Manipulated Cord Blood

Background: We collect and process cord blood with minimal manipulation and label it accordingly for homologous use. We subsequently distribute this product to the clinical side for administration, often to physician offices and medical clinics. The clinical side may use these products as labeled.

We are aware of cord blood products being marketed for a wide range of unapproved uses by “clinics” who feel they should be able to use their stored cells ‘as they want’. We use the term ‘clinic’ loosely, as they may be a physician’s office, a dentist, a chiropractor, a nurse, or sometimes it seems no medical/scientific credentials at all.



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Minimally Manipulated Cord Blood (cont'd)

Question 9: Are we (the manufacturer/distributor) responsible if the clinical facility decides to use the product off-label for nonhomologous use?

FDA/OTP Q9:

“If an establishment does not meet an exception in 21 CFR 1271.15 or if any HCT/P does not meet all the criteria in 21 CFR 1271.10(a) (e.g., due to manufacturing that would entail more than minimal manipulation or because the HCT/P is intended for a non-homologous use), then the product would be regulated as a drug, device, and/or biological product under the Federal Food, Drug, and Cosmetic Act (FDCA) and/or section 351 of the PHS Act, and applicable FDA regulations; in these instances, premarket review (e.g., IND or BLA) will generally be required.

Responsible manufacturers know to whom they are selling their products and the (intended) uses of those products. We do not recognize unknown intended uses.”

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Minimally Manipulated Cord Blood (cont'd)

Question 10: Are there specific FDA regulations we can cite to indicate we cannot release cord blood products for unapproved uses?

FDA/OTP Q10:

“The relevant laws and regulations include the following:

- Federal Food, Drug, and Cosmetic Act section 301 Prohibited Acts and Penalties (21 USC 331);
- Public Health Service Act section 351 Regulation of Biological Products (42 USC 262), which includes the requirement that biological products be licensed; and
- 21 CFR Part 1271, HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS.”

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Minimally Manipulated Cord Blood (cont'd)

Question 11: These so called “clinics” are misleading the general public and sowing misinformation. There appear to be hundreds locally, and thousands across the country. Please update us on what FDA is doing to address these “clinics” using cord blood and other cellular material inappropriately?

FDA/OTP Q11:

“In August 2017, FDA announced an increase in its enforcement and compliance actions against purveyors of unapproved stem cell and related products. Since that time, FDA has engaged in continuous, collaborative efforts with the U.S. Department of Justice to pursue and support FDA’s enforcement actions in federal district and appellate courts, including two injunctions and a seizure.

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Minimally Manipulated Cord Blood (cont'd)

FDA/OTP Q11 (cont'd):

FDA also has taken numerous compliance actions involving those manufacturing or marketing unapproved stem cell or related products. These actions consist of publicly available Warning Letters and Untitled Letters, which put individuals and companies on notice about their violations. In best-case scenarios, Warning Letters and Untitled Letters prompt individuals and companies to rectify violations and commit to complying with the law going forward.

Since August 2017, FDA has issued 28 Warning Letters involving stem cell or related products that violated the Public Health Service Act (PHS Act); the Federal Food, Drug, and Cosmetic Act (FD&C Act); and/or their implementing regulations. FDA issued most of these letters following facility inspections; during these inspections, FDA investigators had documented significant violations of current good manufacturing practice requirements. In

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Minimally Manipulated Cord Blood (cont'd)

FDA/OTP Q11 (cont'd):

addition to the Warning Letters, FDA has issued over 40 Untitled Letters involving stem cell or related products since July 2018. Since December 2018, FDA also has issued over 600 letters to manufacturers, healthcare providers, and clinics in almost all 50 states who may be offering stem cell or related products. These letters notify recipients that they appear to be marketing a product that may be in violation of the PHS Act, the FD&C Act, and/or their implementing regulations.

Finally, FDA has also been very active in promoting stakeholder education and outreach activities for patients, hospitals, healthcare practitioners, manufacturers, and clinics in this field.

While FDA's case-specific enforcement, compliance, education, and outreach activities largely have been successful, these efforts unfortunately have not deterred the continued proliferation of those manufacturing and marketing lucrative unapproved stem cell or related products.”

Hydroxy Ethyl Starch

Background: Some large US manufacturers of approved Hydroxy Ethyl Starch (HES) are suspending or discontinuing manufacture of this product.

Question 12: Does FDA have any recommendations for replacement products for use in cryopreservation of HCT/Ps under IND or BLA in the light of these developments?



FDA/OTP Q12:

“Although not specified, it appears this question is about Hydroxy Ethyl Starch (HES) that may be used in processing and/or cryopreservation of HPC, Cord Blood.

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Hydroxy Ethyl Starch (cont'd)

FDA does not provide recommendations for the use of specific reagents for the manufacture of products. Manufacturers may consider HES from alternative vendors or manufacture processing methods that do not require use of HES.

The Agency generally does not regulate reagents that are used in HCT/P manufacture; however, we recommend the use of FDA approved or clinical grade reagents. HPC, Cord Blood regulated as drugs and/or biological products under the Food, Drug, and Cosmetic Act and/or section 351 of the Public Health Service Act are subject to current good manufacturing practice requirements. For these products, information related to the reagents used in manufacturing processes is provided in the appropriate submission to the FDA for review (e.g., IND or BLA). Please note that any manufacturing changes to existing INDs or BLAs should be reported in an amendment or supplement to the respective applications.

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Hydroxy Ethyl Starch (cont'd)

FDA/OTP Q12 (cont'd):

IND sponsors or BLA applicants are encouraged to discuss these types of changes with the FDA in advance of making a change.”

Question 13: Could you comment on how the agency supports the availability of licensed therapies when there are critical material shortages?

FDA/OTP Q13:

FDA views risk management plans (RMP) to be an important mechanism that stakeholders can use to proactively identify, assess, and mitigate the risks that might lead to a disruption in the supply of drug products, and thus preemptively reduce the financial and resource burden associated with resolving a shortage and problems that may lead to a shortage. The purpose of initiating an RMP is to allow a stakeholder to proactively assess the risks of a drug supply disruption, rather than wait for an actual disruption to

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Hydroxy Ethyl Starch (cont'd)

FDA/OTP Q13 (cont'd):

occur. Please see the FDA draft guidance titled, “Risk Management Plans to Mitigate the Potential for Drug Shortages, Draft Guidance for Industry, May 2022,” for FDA’s current thinking on risk management plans (RMP) (<https://www.fda.gov/media/158487/download>).

FDA believes that RMPs help to ensure that risks with the potential to disrupt the drug manufacturing process, including those risks associated with critical ingredients and materials, and the drug supply chain have been identified, assessed, and mitigated. For example, when developing an RMP, manufacturers should consider supply chain vulnerabilities, such as sole source manufacturers of critical components, ingredients, and materials in a drug product, and identify alternate sources proactively.”

ASK CMS / CLIA

Direct Observation

Background: [42 CFR 493.1413 Standard](#); Technical consultant responsibilities and [42 CFR 493.1451 Standard](#) Technical supervisor responsibilities:

- (b) The technical consultant (technical supervisor) is responsible for—*
 - (8) Evaluating the competency of all testing personnel and assuring that the staff maintain their competency to perform test procedures and report test results promptly, accurately and proficiently. The procedures for evaluation of the competency of the staff must include, but are not limited to—*
 - (i) Direct observations of routine patient test performance, including patient preparation, if applicable, specimen handling, processing and testing;*

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Direct Observation (cont'd)

...

(iv) Direct observation of performance of instrument maintenance and function checks;

(v) Assessment of test performance through testing previously analyzed specimens, internal blind testing samples or external proficiency testing samples;

Question 1: The COVID-19 Pandemic certainly challenged our ability to perform competency in person assessments. Are there general recommendations in regard to CLIA Testing Personnel direct observation for Competency Assessment?

CMS Q1:

“CLIA regulations require that direct observation for Competency Assessment (CA) be performed in person. CMS CLIA is not considering any alternatives for competency at this time as CLIA does not require that CA be done on the same day for all employees, nor does

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Direct Observation (cont'd)

CMS Q1 (cont'd):

it require that CA be done on the same day each year. Competency assessment can be done throughout the entire year by coordinating it with routine practices and procedures to minimize impact on workload.”

Question 2: How can establishments maintain social distancing, such as during the COVID-19 Pandemic, when performing direct observations?

CMS Q2:

“CLIA regulations are not prescriptive on how establishments can maintain social distancing. The CLIA regulations at Subpart J—Facility Administration for Nonwaived Testing contain requirements related to safety. §493.1101 Standard: Facilities states that safety procedures

Direct Observation (cont'd)

CMS Q2 (cont'd):

must be established, accessible, and observed to ensure protection from physical, chemical, biochemical, and electrical hazards, and biohazardous materials. It is the laboratory director's responsibility to ensure that these safety procedures are in place.

CLIA requirements are minimal requirements. Laboratories that obtain CLIA certification by virtue of accreditation by a CMS approved accreditation organization (AO) must follow all the requirements of the accreditation organization (AO), which may be more stringent than the CLIA regulation. In addition, some states have laboratory licensing laws separate from the CLIA regulations that are more stringent than CLIA. Helpful link: [State Agency Contacts](#).”

Direct Observation (cont'd)

Question 3: Are Zoom, Skype, or video recordings acceptable to perform direct observations?

CMS Q3:

“Please refer to response for Q 1. CLIA regulations require that direct observation for Competency Assessment (CA) be performed in person. CMS CLIA is not considering any alternatives for competency at this time as CLIA does not require that CA be done on the same day for all employees, nor does it require that CA be done on the same day each year. Competency assessment can be done throughout the entire year by coordinating it with routine practices and procedures to minimize impact on workload.”



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Direct Observation (cont'd)

Question 4: Specifically related to [§493.1413 \(b\)\(8\)\(v\)](#) and [§ 493.1451 \(b\)\(8\)\(v\)](#), can an assessor evaluate staff test performance by performing a record review of results obtained by the staff of a previously analyzed specimen, internal blind testing sample or external proficiency testing sample? Or must this procedure be direct observation and the staff must retest one of the sample types?

CMS Q4:

“In general competency must be evaluated for each test performed. For example, the various tests used in working up antibodies, such as panels and antigen typing, each need their own competency evaluation that includes the six elements. It is the responsibility of the technical supervisor to develop a competency assessment program that meets the regulatory requirements. There may be different ways to accomplish compliance

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Direct Observation (cont'd)

CMS Q4 (cont'd):

depending on the testing processes used in the laboratory. Training and competency must be performed at each laboratory. Training and competency assessment performed at Laboratory A cannot be used at Laboratory B. If your laboratory obtains its CLIA certification by virtue of accreditation by a CMS- approved accreditation organization, then your laboratory must follow all your accreditor's requirements which may be more stringent than CLIA.”

Electronic Verification of Competency

Background: We have personnel who may travel to another laboratory to perform testing. We use [42 CFR 493.1451\(b\)\(8\)](#) which 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 assessments 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 which includes all current policies, processes, and procedures related to testing which are shared between the system facilities.

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Electronic Verification of Competency (cont'd)

Question 5: 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 that the competency assessment is current and successful?

CMS Q5:

“It is 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, but competency assessment must be performed at each site, and in person.



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Electronic Verification of Competency (cont'd)

CMS Q5 (cont'd):

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

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

Question 6: If the answer to Question 5 is no, what would be a sufficient process for competency and training documentation in the described situation?

CMS Q6:

“The laboratory site must establish and follow policy and procedures for competency assessment. CLIA requirements are minimal requirements. Laboratories that obtain CLIA

Electronic Verification of Competency (cont'd)

CMS Q6 (cont'd):

certification by virtue of accreditation by a CMS approved accreditation organization (AO) must follow all the requirements of the accreditation organization (AO), which may be more stringent than the CLIA regulation.”

Record Review - Frequency

Background: [42 CFR 493.1250](#) **Analytic Systems** describes the monitoring of analytical systems:

Each laboratory that performs nonwaived testing must meet the applicable analytic systems requirements in [§§ 493.1251](#) through [493.1283](#), unless HHS approves a procedure, specified in Appendix C of the State Operations Manual (CMS Pub. 7), that provides equivalent quality testing. The laboratory must monitor and evaluate the overall quality of the analytic systems and correct identified problems as specified in [§ 493.1289](#) for each specialty and subspecialty of testing performed.

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Record Review – Frequency (cont'd)

42 CFR 493.1289 Standard: Analytic systems quality assessment describes an “ongoing mechanism”:

- (a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and when indicated, correct problems identified in the analytic systems specified in §§ 493.1251 through 493.1283.*
- (b) The analytic systems quality assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of analytic systems quality assessment reviews with appropriate staff.*
- (c) The laboratory must document all analytic systems quality assessment activities.*

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Record Review – Frequency (cont'd)

Question 7: What is the frequency of record review by appropriate laboratory personnel that should be performed and documented for the centralized temperature and humidity monitoring system?



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Record Review – Frequency (cont'd)

CMS Q7:

“The laboratory must follow the policies and procedures for the frequency, that are established by the laboratory director. The frequency must be at least that which is recommended by the manufacturer. CLIA requirements are minimal requirements. Laboratories that obtain CLIA certification by virtue of accreditation by a CMS approved accreditation organization (AO) must follow all the requirements of the accreditation organization (AO), which may be more stringent than the CLIA regulation.”

Compatibility Testing - Complexity

Background: [42 CFR 493.1271](#) **Standard:** Immunohematology points to FDA regulations:

(a) ***Patient testing.***

(1) *The laboratory must perform ABO grouping, D(Rho) typing, unexpected antibody detection, antibody identification, and compatibility testing by following the manufacturer's instructions if provided, and as applicable, [21 CFR 606.151\(a\) through \(e\)](#)*

[21 CFR 606.151](#) **Compatibility Testing**

Standard operating procedures for compatibility testing shall include the following:

(c) *Procedures to demonstrate incompatibility between the donor's cell type and the recipient's serum or plasma type.*

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Compatibility Testing – Complexity (cont'd)



...and

[21 CFR 606.3](#) defines:

(j) Compatibility testing - *The procedures performed to establish the matching of a donor's blood or blood components with that of a potential recipient.*

FDA's [CLIA Complexity Database](#) describes:

* HIGH Complexity designation – All test systems, assays, or examinations used in compatibility testing when performed to determine donor/recipient compatibility: recipient & donor ABO group/D (Rho) type/antigen typing, direct antiglobulin test, tests for unexpected antibody detection & identification, & crossmatch procedures are HIGH Complexity. See Federal Register notice, February 28, 1992 [57 FR 7245].

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Compatibility Testing – Complexity (cont'd)



Question 8: Are individuals that do not meet the requirements for high complexity testing qualified to perform compatibility testing using an electronic crossmatch procedure?



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Compatibility Testing – Complexity (cont'd)



CMS Q8:

“The CLIA regulation requiring compatibility testing is found in 42 CFR 493.1271(a), and it refers specifically to 21 CFR 606.151 (a-e). CLIA defers to the FDA because the FDA regulates these immunohematological activities. It is our understanding that in 2001, the FDA broadened the language in 21 CFR 606.151(c) to require compatibility testing “procedures to demonstrate incompatibility between the donor’s cell type and the recipient’s serum or plasma type.” According to the Federal Register background, this change was made to eliminate the reference to serologic testing and allow computer crossmatching. It is also our understanding that the FDA does not make a distinction between the complexity for serological crossmatch and computer crossmatch for the purposes of categorizing complexity. The FDA has categorized ALL IMMUNOHEMATOLOGY DONOR /RECIPIENT

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Compatibility Testing – Complexity (cont'd)



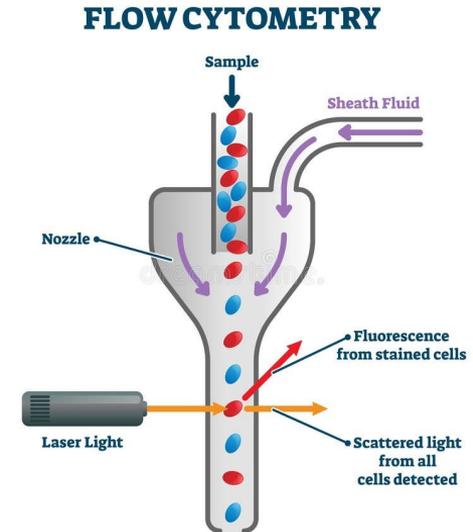
CMS Q8 (cont'd):

COMPATIBILITY PROCEDURES as high complexity. As such, testing Personnel performing activities determining donor/recipient compatibility such as computer crossmatch, selection for compatibility of non-crossmatched blood products (such as platelets, plasma, and cryoprecipitate) must meet the qualifications for high complexity testing personnel.”

Flow Cytometry

Background: Flow cytometry evaluation of CD34+ cell level is necessary for evaluation of the potency/dose of collected hematopoietic progenitor cells used in stem cell transplantation and to determine whether additional products should be collected if the target is not met.

Question 9: Is this testing subject to CLIA regulations?



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Flow Cytometry (cont'd)

CMS Q9:

“According to CLIA Policy Memo [SC Letter11_08.pdf](#), purity and potency tests such as CD34+ are not subject to CLIA. CD34+ testing of hematopoietic progenitor stem cells when used for purity and potency testing of a product is not subject to CLIA. For the purposes of CLIA, a laboratory is defined at 42 CFR §493.2 as ‘a facility for the biological, microbiological, serological, chemical, immunohematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings.’ This testing does not fall under the definition of a laboratory. Such testing when used as a part of the product manufacturing process is under the purview of the FDA.”

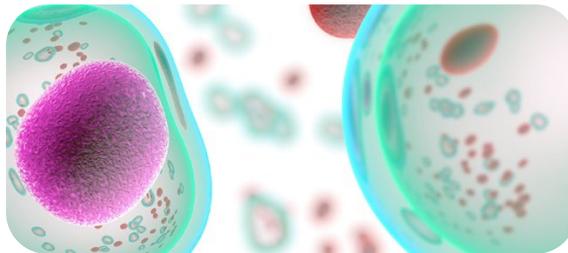
Cellular Starting Material

Background: Our facility collects cellular starting material via apheresis.

Question 10: Is cellular starting material collection via apheresis considered a test/activity for the purposes of CLIA?

CMS Q10:

“For the purposes of CLIA, a laboratory is defined at 42 CFR §493.2 as “a facility for the biological, microbiological, serological, chemical, immunohematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the



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Cellular Starting Material (cont'd)

CMS Q10 (cont'd):

human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings. Facilities only collecting or preparing specimens (or both) or only serving as a mailing service and not performing testing are not considered laboratories.”

Question 11: Do I need to register with CLIA for this activity?

CMS Q11:

“For the purposes of CLIA, a laboratory is defined at 42 CFR §493.2 as “a facility for the biological, microbiological, serological, chemical, immunohematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or

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Cellular Starting Material (cont'd)

CMS Q11 (cont'd):

treatment of any disease or impairment of, or the assessment of the health of, human beings. Facilities only collecting or preparing specimens (or both) or only serving as a mailing service and not performing testing are not considered laboratories.” Therefore, no CLIA certificate is required for collection.”

Question 12: Are there any CLIA requirements for the apheresis machine operators?

CMS Q12:

“For the purposes of CLIA, a laboratory is defined at 42 CFR §493.2 as “a facility for the biological, microbiological, serological, chemical, immunohematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or

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Cellular Starting Material

CMS Q12 (cont'd):

treatment of any disease or impairment of, or the assessment of the health of, human beings. CLIA authorizes regulation of laboratories that conduct testing. Facilities only collecting or preparing specimens (or both) or only serving as a mailing service and not performing testing are not considered laboratories.”

[Ask the FDA and CLIA Transcripts](#)

Thank you!

Contact AABB's Regulatory Affairs Staff at
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