aabb 2024 HOUSTON OCTOBER 19-22

WELCOME

Ask the FDA and CMS/CLIA

2024 AABB Annual Meeting

Faculty Disclosure

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

The following AABB 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 Therapeutic Products (OTP):**
  - **Irma Sison, MD, MBA,** CBER, OTP, Division of Human Tissues, Director
- **Office of Blood Research and Review (OBRR):**
  - **Orieji Illoh MD,** CBER, OBRR, Deputy Office Director
  - **Catherine McGraw, MSN, RN,** CBER, OBRR, Consumer Safety Officer
  - **Racquel East, MS, MLS(ASCP)SBB,** CBER, OBRR, Clinical Laboratory Scientist

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)
- **Lizet Estrada, MLS(ASCP)CM,** Clinical Laboratory Scientist Center for Clinical Standards and Quality (CCSQ), Quality, Safety & Oversight Group (QSOG), Division of Clinical Laboratory Improvement and Quality (DCLIQ)

Look for:

AABB *Weekly Report* sent to your INBOX every Wednesday!

Ask the FDA & CMS/CLIA Transcript
Regulatory > Regulatory Resources > Ask The FDA and CLIA Transcripts

Regulatory Update Toolkits
Searchable PDFs of all Regulatory articles from *Weekly Report*
(includes Regulatory Update Toolkits for: 2019-2020, 2021-2022, 2023-2024)

FDA/OBRR Updates

Orieji Illoh, MD

Deputy Director, Office of Blood Research and Review (OBRR),
CBER, FDA

AABB Annual Meeting, Ask the FDA and CMS/CLIA
October 21, 2024

Disclosure

I have no relevant financial relationships to disclose for this session

Objectives

- Provide relevant updates on activities in FDA and the Office of Blood Research and Review (OBRR)
- Address some commonly asked questions

TRANSCRIPT

Dr Illoh:

“Good afternoon, everyone and thank you once again to AABB for inviting us for this session. Thank you to all for attending and for submitting your questions to us for really thoughtful discussions and responses. We hope you will find this helpful. As Karen introduced, I am the deputy office director in the Office of Blood. What I'll be doing is to just give a really brief update from FDA, mainly from the Office of Blood. I have no financial relationships to disclose. My objectives today is to give you brief updates on our activities on the Office of Blood and FDA, and then also to address some commonly asked questions that we've encountered over the last year.

FDA Reorganization of Foods and Inspection Programs effective October 1, 2024

- **Human Foods Program (HFP)**
  - Realigns the functions of the Center for Food Safety and Applied Nutrition

- **Office of Inspections and Investigations (OII)-**formerly ORA
  - Enables field operations unit to focus on inspections, investigations and imports as its core mission

Inspection activities conducted by OBRR have not changed

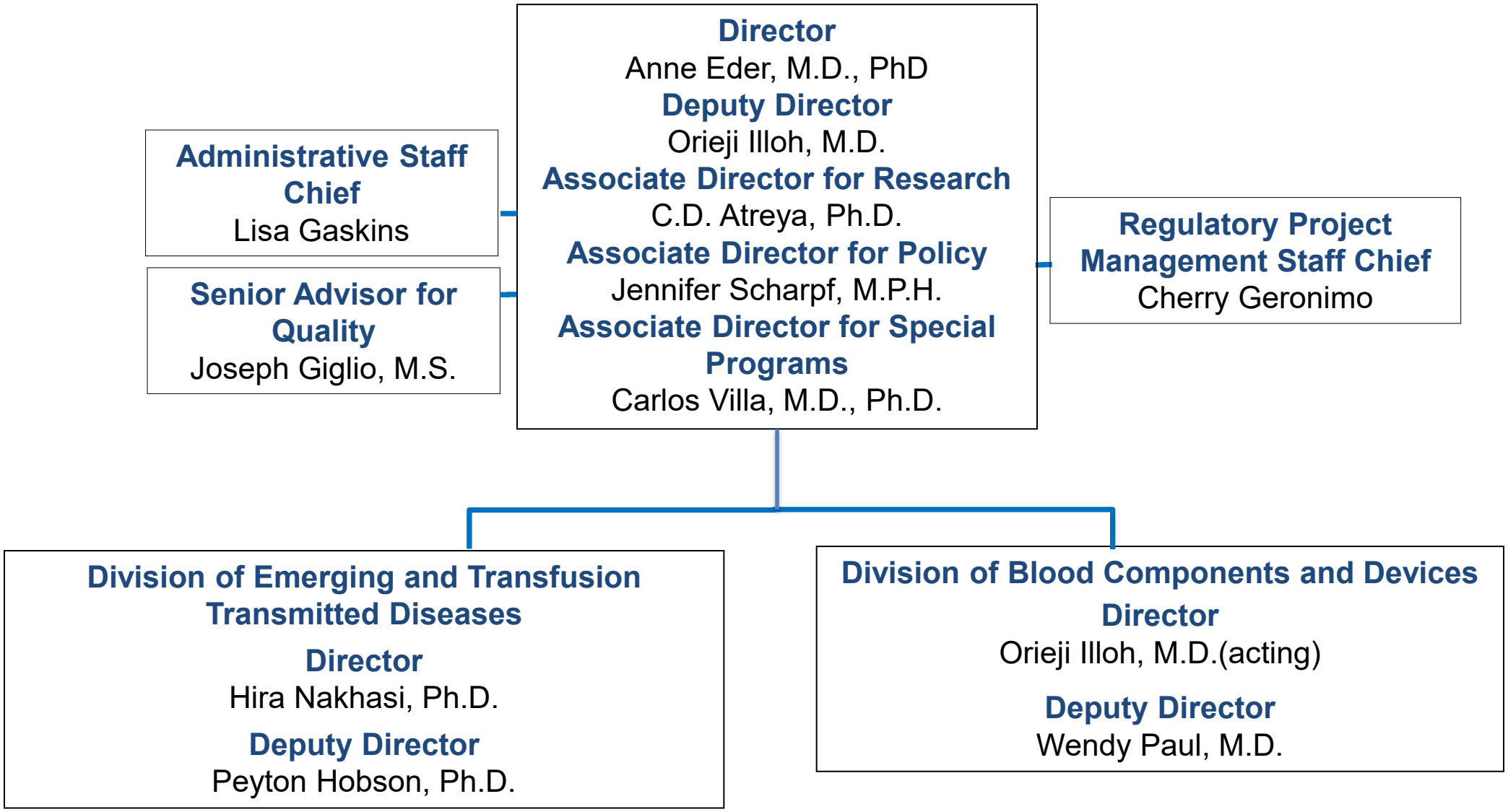
https://www.fda.gov/news-events/press-announcements/fdas-unified-human-foods-program-new-model-field-operations-and-other-modernization-efforts-go

TRANSCRIPT

Dr Illoh (cont'd):

The first update. Some of you might be aware that there was a big reorganization in FDA over the last one year and it became effective October 1st, 2024. This one is the Human Foods Program which realigns functions at the Center for Food Safety and Applied Nutrition, formerly known as CFSAN. The second is the Office of Inspections and Investigations, now OII, formerly known as ORA, which was the Office of Regulatory Affairs. The goal of this reorganization was to enable the operations to focus more on inspections and investigations on imports as its core mission. What I want to emphasize here is that this reorganization does not change the inspection activities within the Office of Blood. We will continue to do the pre-approval and pre-license inspections as we've done. We've gotten a few questions about that, and we wanted to clarify that. If you want more information about the reorganization, I've put a web link here, but I've also been reminded by my colleagues from OII that there will be a session tomorrow, by them about some of these functions and will emphasize more about that.

Office of Blood Research and Review (OBRR)



TRANSCRIPT

Dr Illoh (cont'd):

On this slide here, I just wanted to show our current organization chart in the Office of Blood. We are about 150 staff in the Office of Blood. Dr. Anne Eder is the office director, and she's right here if you've not met her. Please do stop by and speak with her if you would like. Then we have two divisions, the Division of Emerging Transfusion Transmitted Diseases and the Division of Blood Components and Devices. Within the Division of Blood Components and Devices, actually both divisions, we have several branches and labs that participate in research, but with DBCD we also have several branches including the Blood and Plasma Branch, which I'll talk a little bit more about because their work correlates with what you what you do. You most likely have more contact with the Blood and Plasma Branch compared to others. I will mention that we have several staff from our Blood and Plasma Branch here, including our panelists here who will be addressing the questions. If you want to meet them after the session, please do. Before I go through the branches, I also want to just throw in something as well, that we are recruiting a physician for our Division of Blood Components and Devices. If there's interest in that please do stop by and talk with us or refer to our websites as well.

Blood and Plasma Branch (BPB)

- Oversee blood establishment registration
- Review applications for the manufacture of blood components intended for transfusion or further manufacturing
- Conduct inspections (preapproval and prelicensure)
- Develop blood policy
- Advise blood establishments on regulatory issues

Branch Chief:

Richard McBride, MS

Team Leads:

Miriam Montes, MS, MT(ASCP)SBB

Camilla Smith, BS, BB(ASCP)SBB

Review staff: 13

TRANSCRIPT

Dr Illoh (cont'd):

The Blood and Plasma Branch. Some of their functions are listed here. The branch chief, Richard McBride, is also here. It also consists of two team leads, Miriam Montez and Camilla Smith, who could not attend the meeting this year. Also 13 review staff, really great seasoned experienced review staff, that do things like inspections, regulatory reviews of the submissions. We have quite a number here so, thank you for being here, and thank you for all the work you do, inspectional work and also review work for our blood establishments.

Registered and Licensed Blood Establishments (October 2024)

Registered only (e.g., hospital blood banks, transfusion services)	754
Licensed blood collection establishments (65 license holders)	958
Licensed Source Plasma establishments (28 license holders)	1165

TRANSCRIPT

Dr Illoh (cont'd):

Just to snapshot of some of the activities. We have registered hospital blood banks and transfusion services, about 754. This is data from this month. Then we have 958 licensed blood collection establishments. 65, that means 65 license holders and also a couple of licensed Source Plasma establishments, and this continues to grow. We are continuing to see a growth in Source Plasma collections, in particular, over the years.

Biologic License Applications (BLA) and Supplements Reviewed by BPB (0ct 1, 2023- Sept 30, 2024)

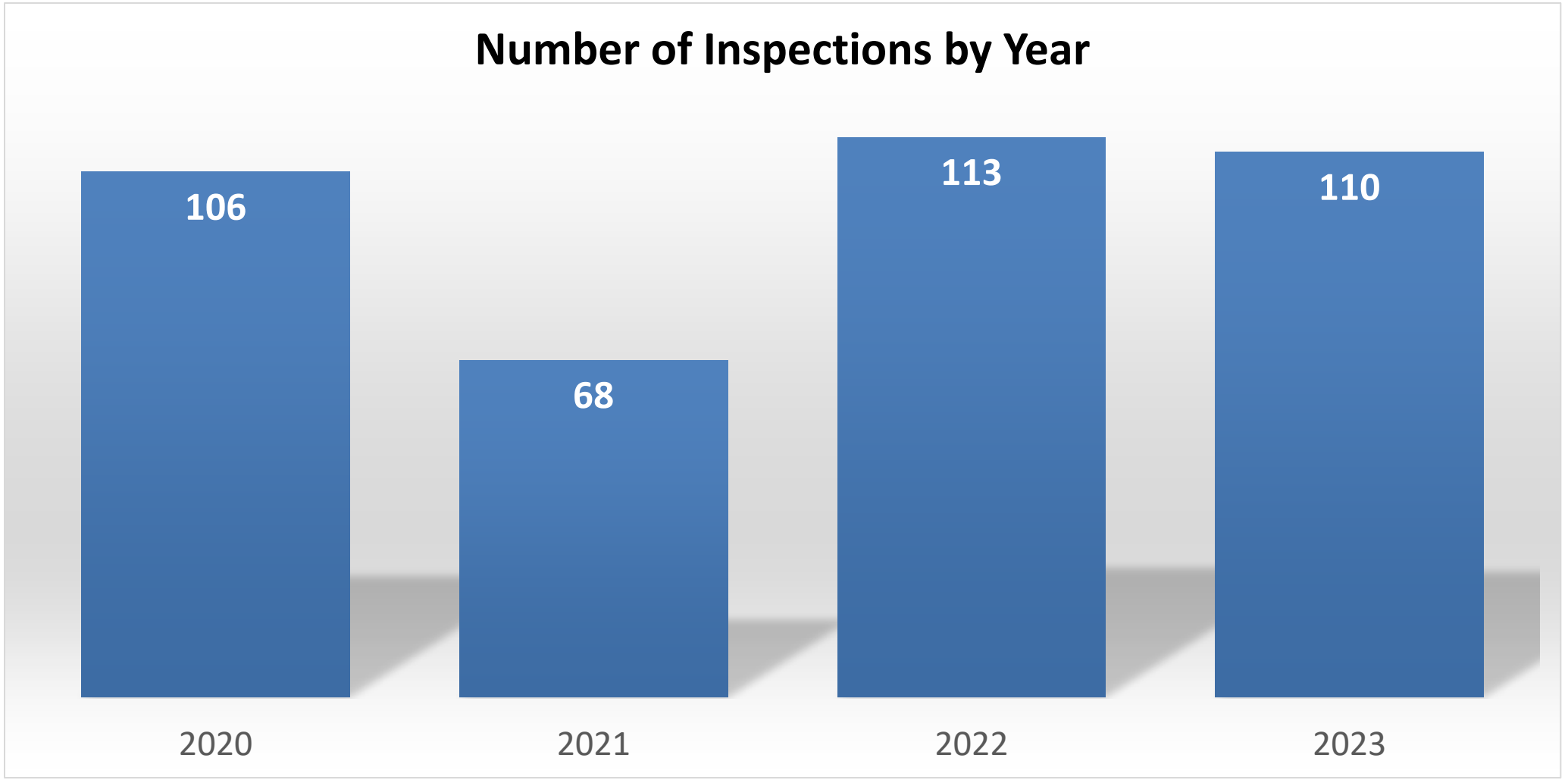
Submission Type	Number
Original BLA	3
Prior Approval Supplement	165
Changes Being Effected in 30 Days Supplement	89
Changes Being Effected Supplement (CBE)	51
Annual Reports	87
Product Correspondence	110

TRANSCRIPT

Dr Illoh (cont'd):

In terms of the regulatory work that is done in the blood and plasma branch, this slide shows the work that's been done over the last one year. I've broken it down here by submission type. You can see here that we have 3 original BLA's which means this is a blood establishment who is applying for a license for the first time. We don't get a lot of that, but that entails a lot of work, including inspections. Then, we also have a lot of prior approval supplements, either for major changes in manufacturing, or opening of new centers which also entails inspections. Then, I also have the other categories here, the CBE-30, CBE Annual Reports and product correspondence. Remember, I did mention we have 13 staff in the Blood and Plasma Branch that do a lot of this work including inspectional activities. So, when you're wondering when they're going to come and inspect my facility, there's a lot going on here.

Inspections Conducted by BPB (2020 to 2023)



TRANSCRIPT

Dr Illoh (cont'd):

In terms of inspections, which I've been talking about, I have here the inspections that have been conducted in the last four years. Since 2018-2019, around that time, we were seeing about 70 to 80 inspections a year. You can see the numbers continue to grow. I think most of those numbers are within the Source Plasma realm, but however, we began to also inspect for lead inspections for pre-approvals or pre-licensure of blood collection establishment since 2023. We're beginning to see also an increase in that number as well. We anticipate more inspections over the next few years.

Commonly Asked Questions

Cold Stored Platelets (CSP)

- In 2023, FDA published Guidance : *Alternative Procedures for the Manufacture of Cold-Stored Platelets Intended for the Treatment of Active Bleeding when Conventional Platelets Are Not Available or Their Use Is Not Practical*

- We continue to receive questions about very specific scenarios regarding the use of CSP
  - The exceptions and alternative procedures provided under 21 640.120 (b) in the guidance apply only to CSP intended for the treatment of active bleeding when conventional platelets are not available, or their use is not practical

TRANSCRIPT

Dr Illoh (cont'd):

Now I'll go to the commonly asked questions. Some of you will be familiar with some of these questions. One is cold-stored platelets. As many of you are aware, FDA published guidance titled, Alternative Procedures for the Manufacture of Cold-Stored Platelets Intended for the Treatment of Active Bleeding when Conventional Platelets Are Not Available or Their Use Is Not Practical. Followed by this guidance, Dr. Carlos Villa, who is also at this meeting, gave a nice AABB webinar about the guidance and clarified some questions. We continue to get questions about this guidance and many of them are regarding specific scenarios in your blood establishment or Transfusion Service. I just want to emphasize again that the guidance is giving exceptions and alternative procedures under 21 CFR 640.120(b), which applies to CSP intended for treatment of active bleeding when conventional platelets are not available or their use is not practical. In terms of the questions we've been getting, a lot of them have been like, "My transfusion service is here. Our blood bank is one block away, blah, blah, blah, and so on and so forth. Can we use cold-stored platelets?"

Cold Stored Platelets (cont.)

- We expect that transfusion services will develop SOPs to define the circumstances based on their unique characteristics
    - Consider current supply, anticipated shortages, transport and storage logistics, and any other factors that affect the ability to provide platelets to bleeding patients
- FDA will continue to assess the available data to determine whether changes to the recommendations described in this guidance are appropriate

TRANSCRIPT

Dr Illoh (cont'd):

We just wanted to clarify that we really don't intend to review each scenario. What we've been telling individual transfusion services, and some of you have heard sessions, particularly in this meeting, about the different settings for different transfusion services, not one fits all. We really expect transfusion services to develop their own SOPs to define the circumstances based on their unique characteristics. You should decide when you think platelets are not available or not practicable for use, depending on your transfusion service and develop that in your SOPs. Some of the things that you can consider are your current supply, your anticipated shortages, transport and storage logistics and other factors that can affect the ability to provide platelets to your bleeding patients. As we mentioned in the guidance, FDA will continue to assess the available data. We're aware of clinical trials, that we really encourage, and look forward to reviewing the data. We'll determine whether changes to recommendations and guidance are appropriate.

Shipment of Unlicensed Blood Components in Emergencies

- During emergencies and local shortages, a healthcare facility in any state can send unlicensed (and licensed) blood components to other facilities in the same state
- If a patient has a documented urgent medical need for blood components, the healthcare system can send unlicensed units for transfusion to the patient in another state
  - Please refer to FDA Compliance Policy Guide (CPG) 220.100 entitled "Interstate Shipment Biologicals for Medical Emergency, at weblink: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cpg-sec-220100-shipment-biologicals-medical-emergency

TRANSCRIPT

Dr Illoh (cont'd):
Another common question we got this year was about shipment of unlicensed blood establishments in emergencies. This followed things like the cyber-attack, that we were all aware of with one of our blood centers, and also weather-related issues. What we want to clarify regarding this question is that during emergencies, or local shortages, a healthcare facility in any state can send unlicensed and licensed blood components to other facilities from the same state. I think there's another question about this in Ask the FDA, so that would be clarified also for licensed. Of course, if a patient has a documented urgent need for blood components, the healthcare system can send unlicensed units for transfusion to the patient in another state. We refer you to what we call the CPG. I have the web link here, but this will be available in the transcript, and I think it's also available on the slides on the app if you want to look at that.

Blood Donor Testing Requirements (21 CFR 610.40)

Blood establishments must test each donation for evidence of relevant transfusion-transmitted infections

Question to FDA: Is it acceptable to not perform testing on collections determined not suitable for transfusion or manufacturing that we intend to discard?

TRANSCRIPT

Dr Illoh (cont'd):

Blood donor testing under 21 CFR 610.40. Lots of questions about this. The questions have come in different flavors, but they're about the same, so I'm going to maybe address this in a broader aspect. Under 21 CFR 610.40, blood establishments must test each donation for evidence of relevant transfusion-transmitted infections. The questions we've gotten, generally, “Is it acceptable to not perform testing on collections determined not suitable for transfusion or manufacturing when we intend to discard the unit?” I'm going say generally the answer is “No”.

Blood Donor Testing Requirements- FDA Response

- Per 21 CFR 610.40, blood establishments that collect blood and blood components must test each donation for evidence of infection and, if a reactive screening test result is obtained, perform further testing
- The rationale to test or not test cannot be based on the intent to discard components from a donation
- We recognize that there are occasions when there may be insufficient volume of donated blood to perform RTTI testing, as required

TRANSCRIPT

Dr Illoh (cont'd):

Per the regulations, 21 CFR 610.40, blood establishments that connect blood and blood components must test each donation for evidence of infection, and if a reactive screen test result is obtained, perform further testing. The goal of this of course, is to prevent the distribution of an unsuitable unit because of a positive test, but also to test the donor and determine whether they need to be deferred from future donations. The rational to test cannot be based on the intent to discard components from donation.

Blood Donor Testing Requirements- FDA Response cont.

- Blood establishments should define in their SOPs when the collected volume of donated blood is insufficient and they cannot perform RTTI testing (i.e., “QNS” or quantity not sufficient).
- We also encourage blood establishments to inform the donor that RTTI testing cannot be performed if the collected volume is insufficient

TRANSCRIPT

Dr Illoh (cont'd):

We recommend that blood establishments define in their SOP's when the collection volume of donated blood is insufficient, and they cannot perform RTTI testing. Like I mentioned, some call it QNS. We encourage blood establishments, we do know that you do inform your blood donors that you may not perform testing, but I think it will be important to inform your donors that RTTI testing may not be performed if the collection volume is insufficient. That's really it for the most commonly asked questions. I want to give time to my colleagues to address some of the questions that you submitted, so you can get responses to that.

Additional Information

- **Contacts**
  - For OBRR regulatory submissions
    - Contact Regulatory Project Management Staff Cherry.Geronimo@fda.hhs.gov
  - For inquiries related to blood manufacturing
    - BPB Inquiries mailbox: CBEROBRRBPBInquiries@fda.hhs.gov
- **Blood Guidances:** https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/blood-guidances
- **CBER Guidance Agenda:** https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/guidance-agenda-guidance-documents-cber-planning-publish-during-calendar-year-2024

TRANSCRIPT

Dr Illoh (cont'd):

The last slide here has some additional information that you may find helpful. If you have questions about your regulatory submissions, we do run that through our regulatory project management group, and I have here the contacts of the branch chief of that group. For inquiries related to blood manufacturing, which we get a lot of, and we attempt to address them in a timely manner, please do send them to the long e-mail it's written here. We will keep that also keep that on the slides here. I think a lot of you may be familiar with this e-mail address now. I also put here our link for our blood guidances. I also wanted to mention that we just published a guidance regarding Buffy Coat, more towards manufacturers of containers of Buffy Coats collections. Of course, if you want to manufacture blood components with the Buffy Coat method, you need approved bags to do that. Our first step is to put out guidance on what you should do in terms of the manufacturer to submit to FDA. We'll welcome comments about that guidance before we finalize it. Then the last bullet has our guidance agenda. It tells you what we're planning to publish in the future in terms of guidance and we update that I believe twice a year. That's it for me. Thank you really for coming to the session and I hope you'll find it helpful."


FDA
U.S. FOOD & DRUG
ADMINISTRATION

ASK THE FDA

Blood and Blood Components

Hepatitis A – Local Restaurant

Background: A donor reported that he had eaten at a local restaurant where a food handler tested positive to Hepatitis A. The donor received notification that the local Health Department recommended Hepatitis A vaccines for those individuals that dined in/carried out during a 2-week time frame. We have followed our current SOPs/policies concerning donor deferral/lookback/post donation information for this situation without any issues.

Cont'd on following page

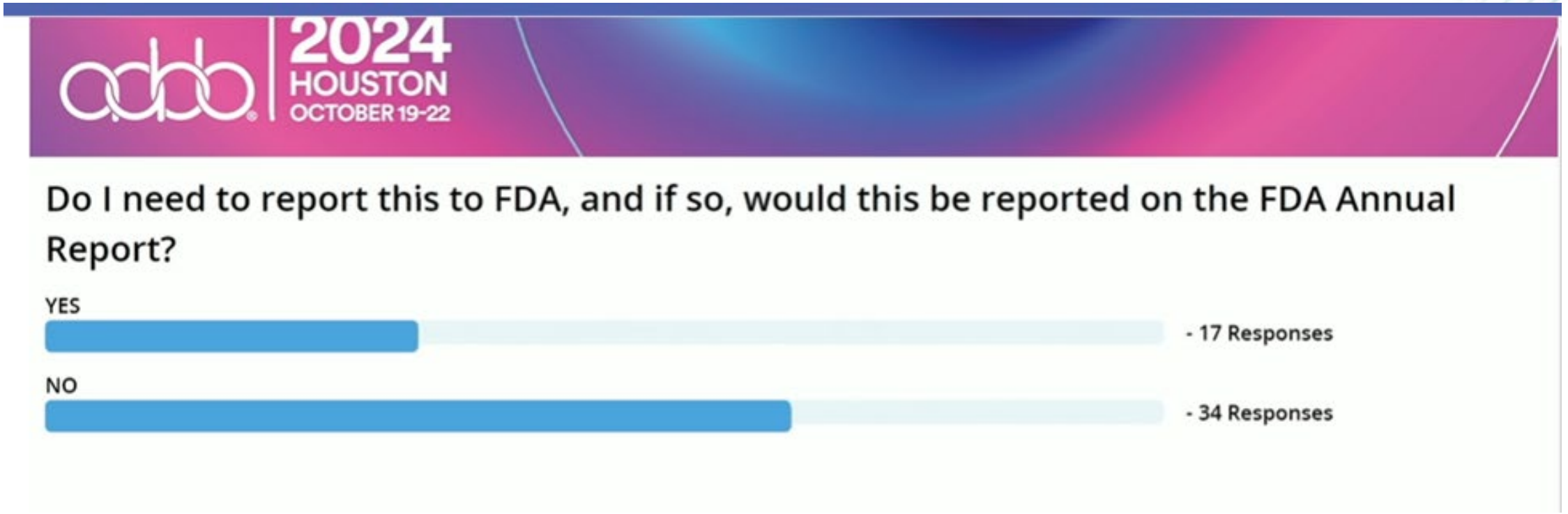
Hepatitis A – Local Restaurant *(cont'd)*

FOR AUDIENCE RESPONSE:

Question 1: Do I need to report this to FDA, and if so, would this be reported on the FDA Annual Report?

Hepatitis A – Local Restaurant *(cont'd)*

AUDIENCE RESPONSE:



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Hepatitis A – Local Restaurant *(cont'd)*

FDA/OBRR Response Q1:

"You do not need to report this occurrence to FDA in your annual report or as a biologic product deviation (BPD).

21 CFR 601.12(d) describes requirements for an annual report. Changes in manufacturing that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product must be reported in an annual report. You do not need to report this event in your Annual Report because it does not represent a change in manufacturing.

And, as stated in our Guidance: Biological Product Deviation Reporting for Blood and Plasma Establishments (March 2020), you are not required to submit this report, when you receive information, after a donation, that would have resulted in deferral of the donor had you known the information at the time of the donation. Such postdonation information is not reported as a BPD, as in this scenario."

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ABO/Rh Testing Incident

Background: Our donor testing lab (we send out our donor screening tests) informed us of an ABO/Rh testing incident. They discovered the issue, corrected it and re-tested all donor samples affected. They will be filing a report with the FDA for their units that were distributed prior to the completion of re-testing. Our facility did not distribute any units prior to the completion of re-testing.

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ABO/Rh Testing Incident *(cont'd)*

FOR AUDIENCE RESPONSE:

Question 2: Am I correct that I do not need to file a BPDR because this error was corrected prior to distribution of our units?

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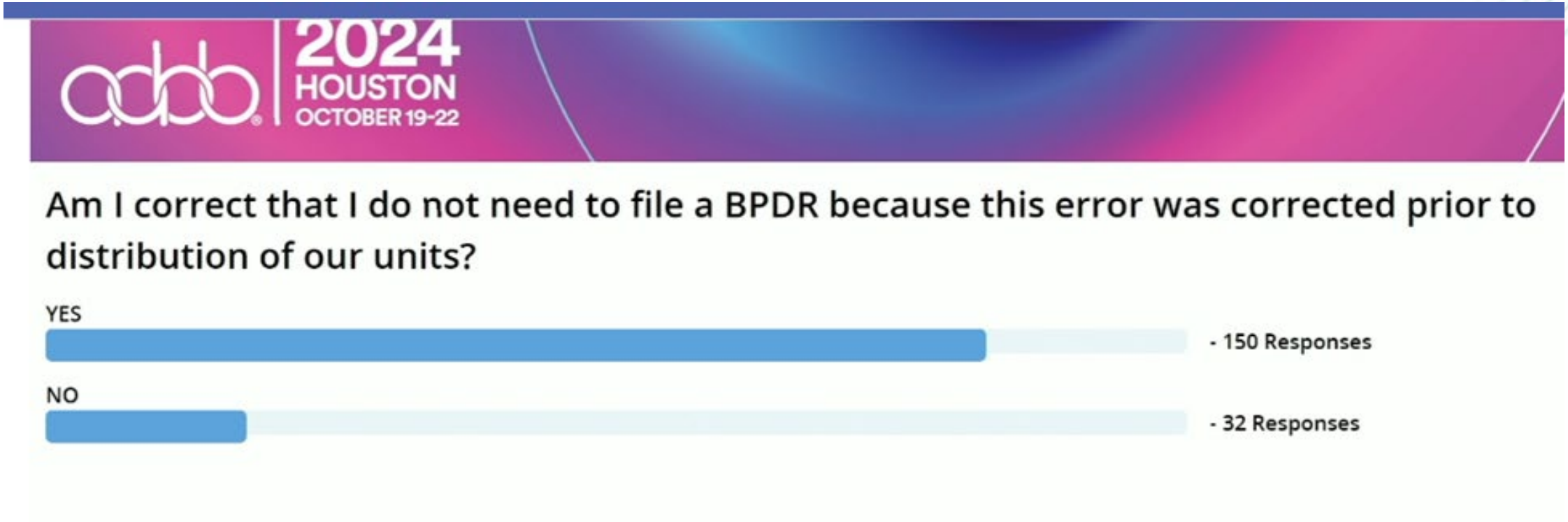
ABO/Rh Testing Incident *(cont'd)*

AUDIENCE RESPONSE:



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ABO/Rh Testing Incident *(cont'd)*

FDA/OBRR Response Q2:

"According to the guidance, you are not required to submit a report when you did not distribute potentially affected products, regardless of the event. Because you did not distribute any units before completion of retesting, the event is not reportable as a BPD."

Cont'd on following page

ABO/Rh Testing Incident *(cont'd)*

FOR AUDIENCE RESPONSE:

Question 3: Do I need to report this event on our FDA Annual Report?

Cont'd on following page

ABO/Rh Testing Incident *(cont'd)*

AUDIENCE RESPONSE:

Cont'd on following page

ABO/Rh Testing Incident *(cont'd)*

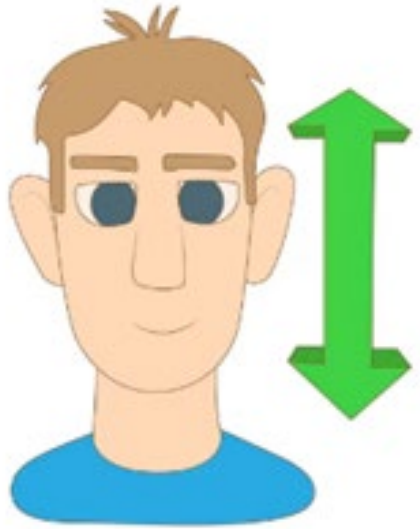
FDA/OBRR Response Q3:

"You do not need to report this event in your Annual Report."

Donor Responses – Verbal vs Nonverbal

Background: During our donor eligibility and screening process we privately and verbally address the donor to ask the DHQ questions or follow-up questions from the flowchart.

Question 4: Must the donor respond verbally to the donor screening questions or is a head nod "yes" or "no" adequate?



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Donor Responses – Verbal vs Nonverbal *(cont'd)*

FDA/OBRR Response Q4:

"Blood establishment procedures should describe how to document donor responses to screening questions. Typically, this is done verbally. If there are situations when a donor cannot respond verbally, blood establishments should describe how they will determine donor eligibility based on a non-verbal response to the donor history questions."

Donor Eligibility – Donor Does Not Recall Reason for Deferral

Background: 21 CFR 630.35 *Requalification of previously deferred donors* states the conditions under which a donor may be requalified.

On occasion a donor presents and states they were deferred or had received a letter stating they were deferred and do not remember why. The blood center where they donated is no longer in operation or the reason for deferral cannot be located.

Question 5: Is there a pathway to re-enter this donor if they meet all current screening criteria and all testing requirements?

Cont'd on following page

Donor Eligibility – Donor Does Not Recall Reason for Deferral *(cont'd)*

FDA/OBRR Response Q5:

"If information about a previous deferral reported by the donor is unclear or unknown, the responsible physician may evaluate and determine whether the donor is eligible to donate. Blood establishment procedures should describe your process for determining that a deferred donor can be requalified to be eligible to donate blood and blood components."

Donor Eligibility – Gene Therapy

Background: FDA's "What is Gene Therapy" page provides the definition:

"Gene therapy is a technique that modifies a person's genes to treat or cure disease."

Question 6: What are FDA's recommendations for blood donor deferral following gene therapy, if the therapy has been successful and the donor states they feel healthy and well?

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Donor Eligibility – Gene Therapy *(cont'd)*

FDA/OBRR Response Q6:

"FDA does not have specific recommendations on donor deferral following gene therapy. The blood donor must meet all eligibility requirements. The blood establishments' responsible physician should determine if the treatments received by a donor with a history of gene therapy identify any issues that may warrant donor deferral.

The responsible physician must consider the health of the donor and the effect of the gene therapy on the safety purity and potency of the product."

Donor Eligibility – Arm Inspections

Background: Our facility recently underwent an inspection which resulted in a discussion item related to arm inspection.

21 CFR 630.10(f)(6) Skin examination requires:

> *"(i) The donor's phlebotomy site must be free of infection, inflammation, and lesions; and*
> *(ii) The donor's arms and forearms must be free of punctures and scars indicative of injected drugs of abuse."*

Question 7: Is it FDA's expectation that both the anterior and posterior aspects of the donor's arms and forearms be inspected for scars indicative of drug use?

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Donor Eligibility – Arm Inspections *(cont'd)*

FDA/OBRR Response Q7:

"Yes. The regulations state that the arms and forearms must be free of indications of IV drug use and do not limit the examination to only certain areas of the arm and forearm. Blood establishment procedures must describe how they will inspect the donor's arms and forearms for indication of drugs of abuse."

Donor Center Closure

Background: 21 CFR 606.160(e)(2) – requires:

> "*a cumulative record of donors deferred from donation…because their donation tested reactive…for evidence of infection…*"

During the 2023 Ask the FDA, the agency noted 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."*

Our donor center is closing. The center is not being bought out or merged with another donor center. We are permanently ceasing collections at the end of the month.

Question 8: What is our obligation for record retention and in particular indefinite record retention?

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Donor Center Closure *(cont'd)*

FDA/OBRR Response Q8:

"First, we want to clarify that our response to the 2023 question related to a different situation than what is described in this question.

The 2023 question was generally about record retention requirements for a blood center in operation. In the situation described in this scenario, the establishment is permanently ceasing operations.

Blood establishments must maintain records of each significant step in the collection, processing, compatibility testing, storage, and distribution of each unit of blood and blood components. This requirement includes donor records under 21 CFR 606.160 (a), (b), and (e), and the retention interval for such records are specified under 21 CFR 606.160(d). The purpose of retaining donor deferral records is to determine future donor eligibility."

Donor Center Closure *(cont'd)*

FDA/OBRR Response Q8 *(cont'd)*:

"The regulations do not describe record retention requirements when an establishment permanently ceases collections. If there are no other establishments under common management, then you are not required to retain indefinitely the deferred donor records under 606.160 (e). You must retain records according to the schedule in 606.160 (d) as long as the blood component is available.

We recommend that you also review the requirements from other peer-based accreditation/certification organizations."

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Validation of a New Apheresis Collection Process

Background: Our licensed facility is getting ready to perform a software upgrade which will require revalidation at four of our individual collection sites located in a common geographic area. All locations will be on the same validation plan and SOPs. Each location will continue to follow current regulations and recommendations established for an apheresis license submission to FDA. Our plan is for each of the locations to contribute to the validation testing (e.g., for validation testing of 60 RBC components, 4 individual locations may each contribute 15 components). This would reduce the overall burden of validation testing.

Question 9: Would FDA accept this type of validation plan by geographic area rather than by individual apheresis locations?

Cont'd on following page

Validation of a New Apheresis Collection Process *(cont'd)*

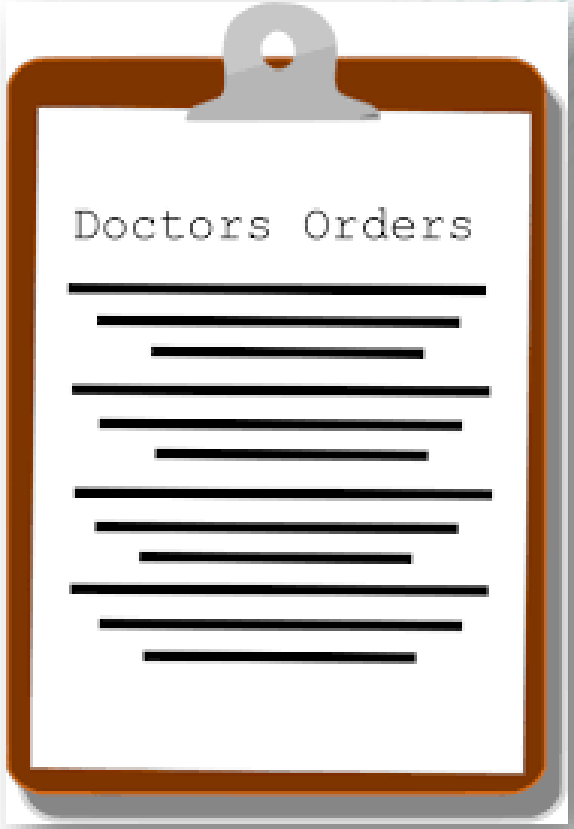
FDA/OBRR Response Q9:

"The information provided in the scenario is not sufficient to determine the extent of validation that might be required. FDA recognizes that software upgrades vary in scope. While often minor, the upgrades may be major changes. We recommend that you engage with your device manufacturer to determine the appropriate validation protocol to qualify the apheresis devices for use after a software upgrade."

Blood Warmer – Medical Order

Background: Blood warmers are medical devices used to warm blood before or during transfusion. Improper use can lead to complications such as hemolysis.

Question 10: Does the use of a blood warmer require a physician order?



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Blood Warmer – Medical Order *(cont'd)*

FDA/OBRR Response Q10:

"The instructions for use (or IFU) of blood warmers state that the device "is intended to be used by healthcare professionals in hospital, clinics and field environments, to help prevent hypothermia."

The regulations do not stipulate whether a physician must write an order. The facility should determine a process for the use of blood warmers to comply with the instructions for use."

Filtration During Administration

Background: 21 CFR 606.122 Circular of Information requires the *Circular* include the following information:

(b) Instructions to use a filter in the administration equipment.

Our Transfusion Service filters pediatric aliquots of RBCs prior to issue to the NICU, nursery, or pediatric floor.

Question 11: Does “in the administration equipment” mean the RBC’s must be filtered again as they are administered to the patient at the bedside?

Cont’d on following page

Filtration During Administration *(cont'd)*

FDA/OBRR Response Q11:

"The preparation method for pediatric aliquots may vary among institutions. As noted in the Circular of Information, "All blood components must be transfused through a filter designed to remove clots and aggregates (generally a standard 150- to 260-micron filter)." If the component was filtered during aliquot preparation, you may not need to filter it again. Your medical director should determine whether it is necessary to filter the component at the bedside."

Inventory Challenges – Helping Other Transfusion Services

Background: We are an FDA Registered Transfusion Service. Occasionally we will receive calls from local and/or regional Transfusion Services asking if we can help them out with red cells or platelets during emergency situations such as an MTP. We receive our blood from an FDA licensed blood collection facility and all components are labeled with their facility license number.

As a registered-only Transfusion Service, we plan to ship blood to another hospital using shipping containers validated by our blood supplier. They will be packed with ice exactly as normally received from our supplier, and they are received by the other hospital within the validated timeframe for the container.

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Inventory Challenges – Helping Other Transfusion Services *(cont'd)*

FOR AUDIENCE RESPONSE:

Question 12: Is this an acceptable process?

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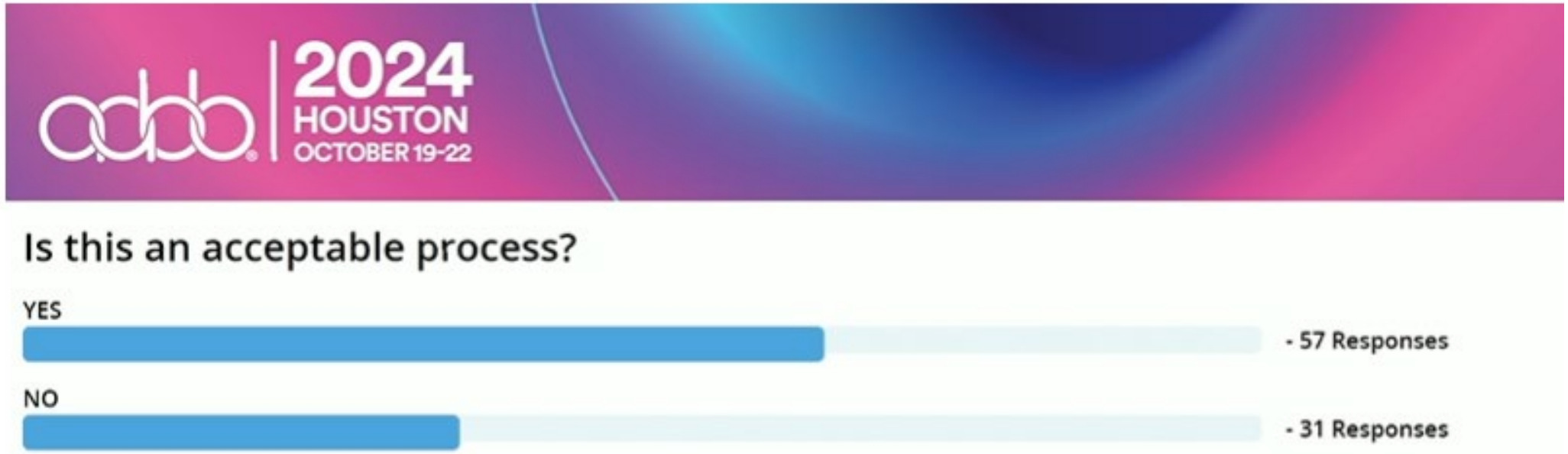
Inventory Challenges – Helping Other Transfusion Services *(cont'd)*

AUDIENCE RESPONSE:



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Inventory Challenges – Helping Other Transfusion Services *(cont'd)*

FDA/OBRR Response Q12:

"Yes, using validated shipping containers to ship blood products within the validated time frame for the container is an acceptable process to send licensed blood components to another hospital during an emergency.

We encourage you to assess the approach that you will use in your emergency preparedness plans and standard operating procedures to ensure that you are able to ship blood at the required temperatures."

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Inventory Challenges – Helping Other Transfusion Services *(cont'd)*

FOR AUDIENCE RESPONSE:

Question 13: As a registered-only Transfusion Service, can we ship blood labeled with our blood supplier's license number across state lines to another hospital as well as to hospitals within our state?

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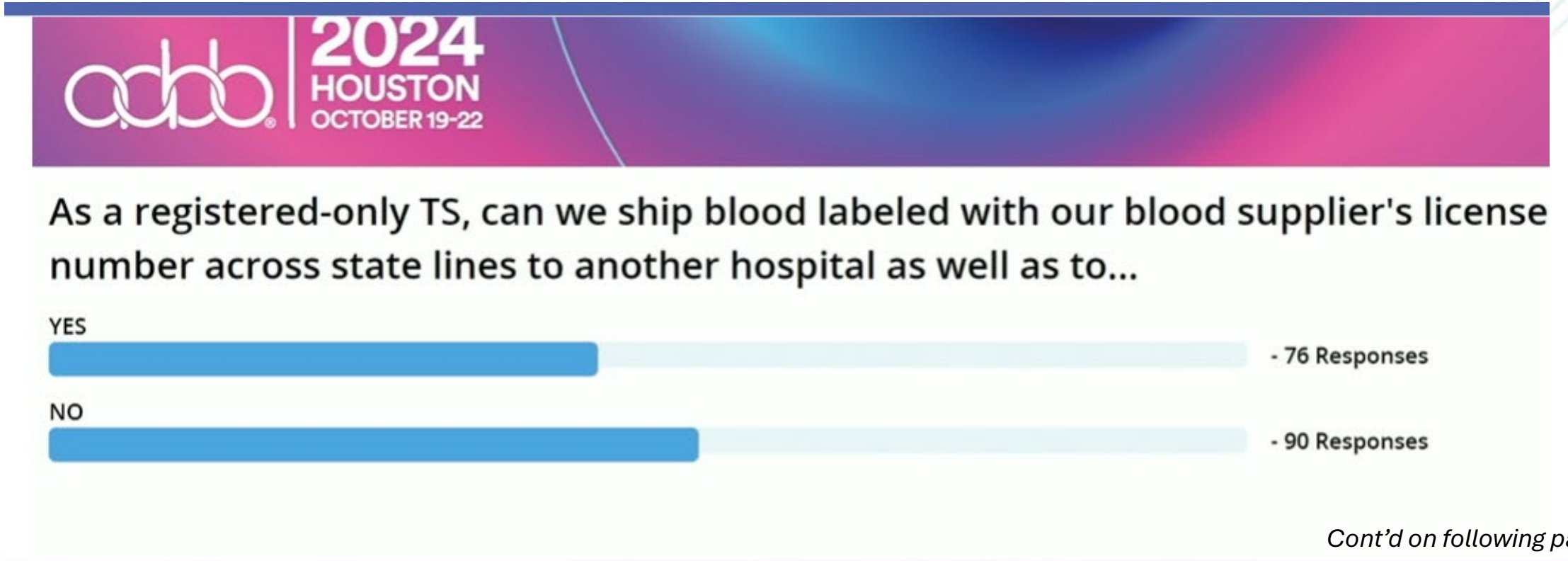
Inventory Challenges – Helping Other Transfusion Services *(cont'd)*

AUDIENCE RESPONSE:



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Inventory Challenges – Helping Other Transfusion Services *(cont'd)*

FDA/OBRR Response Q13:

"Yes. A healthcare facility that has an inventory of blood from a licensed blood center can transport those units to other healthcare facilities in the same state and in other states during an emergency, provided the blood products have the FDA-license number of the manufacturer on the label."

Return and Reissue of Blood

Background: Red blood cells have been placed in a mobile storage container validated to maintain a temperature of 1 to 6 C for 10 hours. The cooler was issued to the operating room and returned to the Transfusion Service 6 hours after issue. The container closures are intact, segments are attached, and inspection is consistent with the requirements of 21 CFR 640.5(e). *The temperature of each unit upon return to the Transfusion Service is 4 C.*

Cont'd on following page

Return and Reissue of Blood *(cont'd)*

Scenario 1: A datalogger has been placed in the storage container to continuously monitor the temperature of the container. The datalogger shows no breach above 6 C.

Scenario 2: An FDA 510(k) cleared indicator device designed to continuously monitor temperature between 1 to 10 C has been applied to each unit and does not show a breach above 10 C.

Scenario 3: Conditions are the same as in Scenario 2, except no indicator device has been applied to each unit.

Question 14: Do each of these scenarios meet FDA requirements for the reissue of blood? Please explain why or why not.

Cont'd on following page

Return and Reissue of Blood *(cont'd)*

FDA/OBRR Response Q14:

"The hypothetical scenarios, as presented, lack sufficient detail for a yes/no answer and any such response might be misleading in the future. Consequently, we will answer this question by reviewing the criteria that should be met regarding inventory management and practice in a hospital. The Transfusion Service and hospital must make the assessment and decision if the units are suitable for reissue.

The Transfusion Service SOPs must define how they will monitor and maintain blood components in storage and during transport at the required temperatures and document the acceptability of the stored or transported blood components for issue or reissue.

Storage containers/coolers used for storage or for transport of Whole Blood and blood products should be validated and qualified for their intended use.

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Return and Reissue of Blood *(cont'd)*

FDA/OBRR Response Q14 *(cont'd)*:

The scenario refers to "mobile storage containers." Since the intended use is storage, then the containers/coolers must be validated with supportable performance data to verify the process maintains the temperature at 1 to 6 C per 21 CFR 610.53(b) for a defined maximum storage period. Consequently, if the following is true, the units are acceptable for reissue:

- the coolers were adequately monitored and
- there is supporting evidence and documentation that the blood components were stored at 1 to 6 for the defined storage period.
- The blood components are received at an acceptable temperature and visually inspected to determine if they are suitable for reissue."

Licensed Donor Screening Tests

Background: The recently approved blood donor malaria testing assay, (and most blood donor screening assays), contain language in the package insert which states "*For in vitro diagnostic use only*" followed shortly thereafter by the phrase, "*This test is not intended for use as an aid in diagnosis of Plasmodium infection*." These two statements seem to be contradictory.

Many donor deferral decisions are based on whether a donor has been "diagnosed" with a certain infection (e.g. malaria, *babesia*, *T. cruzi*).

Question 15: Why is a test labeled as for "diagnostic use only," not intended to "aid in diagnosis"?

For in vitro diagnostic use only

Cont'd on following page

Licensed Donor Screening Tests *(cont'd)*

FDA/OBRR Response Q15:

"The terms might seem contradictory, but they have a specific regulatory meaning that is clearly defined in the regulations. So, we will explain their meaning in the context of the regulations and then in simplified terms.

In vitro diagnostic products, referred to as IVDs, are defined in 21 CFR 809.3, as those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. This means that IVDs are used not only to diagnose a disease, but also for screening, monitoring, prognosis, or other intended uses.

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Licensed Donor Screening Tests *(cont'd)*

FDA/OBRR Response Q15 *(cont'd)*:

All blood donor screening tests for transfusion-transmitted infections meet the definition of an IVD. All blood donor screening test labels include the statement "For In Vitro Diagnostic Use", or the abbreviation "IVD" because the regulation (21 CFR 809.10(a)(4)) specifically requires such a statement as part of warnings and precautions for users.

In other words, all blood donor tests to screen healthy volunteers are IVDs by the regulatory definition; but not all IVDs are evaluated for an intended use as an aid to diagnose disease in patients. The labeling claim for the intended use will depend on the data that support its clinical use."

Cont'd on following page

Licensed Donor Screening Tests *(cont'd)*

Question 16: For purposes of donor eligibility, would a confirmed positive test using an FDA licensed donor screening test constitute a diagnosis?

FDA/OBRR Response Q16:

"The results of blood donor screening tests are not sufficient and generally do not constitute a diagnosis. The Intended Use (IU) of the IVD describes what uses of the device are supported by data demonstrating that the device is safe and effective, for example, for screening blood donors or for use as an aid in diagnosis.

The intended use statement on blood donor screening tests specifically notes that the tests are not for diagnostic use as they have not been validated for that purpose. An individual who has a reactive result on a donor screening test has not been diagnosed with the disease. Diagnosis of a disease or condition in an individual requires testing and confirmation with tests validated and authorized for that use, in accordance with the intended use of the IVD and its instructions for use, and clinical correlation to interpret the results of all testing performed."

Registration – Sedimentation of Red Blood Cells

Background: 21 CFR 640.16 Processing states:

"(a) Separation. Within the timeframe specified in the directions for use for the blood collecting, processing, and storage system used, Red Blood Cells may be prepared either by centrifugation, …or by normal undisturbed sedimentation..."

Our Transfusion Service is not FDA registered. We maintain an inventory of Whole Blood CPDA-1 for transfusion. Our plan is to separate the RBCs following a validated procedure using "undisturbed sedimentation" within one week of expiration. This is within the specified timeframe for the collection, processing, and storage system used. The blood will be continuously stored at 1-6 C during sedimentation. Once the plasma has been separated and discarded, the component will be appropriately ISBT-128 labeled.

Cont'd on following page

Registration – Sedimentation of Red Blood Cells *(cont'd)*

Based on the examples provided in the 2019 Compliance Program Guidance Manual, Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors, page 10:

A transfusion service may also perform the processes below without registering with FDA:

- *Prepare recovered Plasma or Red Blood Cells from Whole collected by a blood bank or blood center*

Cont'd on following page

Registration – Sedimentation of Red Blood Cells *(cont'd)*

FOR AUDIENCE RESPONSE:

Question 17: We interpret this to mean we do not need to register with FDA to prepare RBCs from Whole Blood by sedimentation. Is our interpretation correct?

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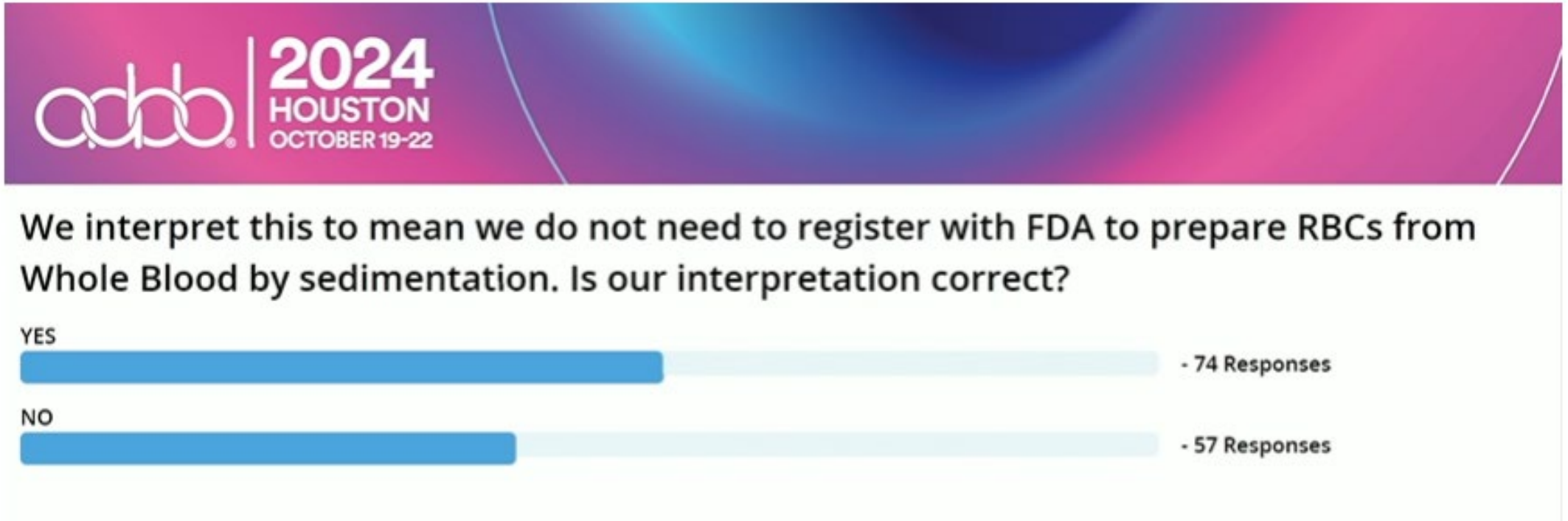
Registration – Sedimentation of Red Blood Cells *(cont'd)*

AUDIENCE RESPONSE:



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Registration – Sedimentation of Red Blood Cells *(cont'd)*

FDA/OBRR Response Q17:

"The interpretation is correct. Per 21 CFR 607.65(f), Transfusion Services that perform compatibility testing and transfusion of blood and blood components, to include the preparation of Red Blood Cells for transfusion, are exempt from FDA registration and blood product listing, provided they are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (42 U.S.C 263a) and 42 CFR part 493, or have met equivalent requirements as determined by the Centers for Medicare and Medicaid Services (CMS)."

FDA Registration – Product Listing

Background: The Blood Establishment Registration (BER) instructions for Completing the Electronic Blood Establishment and Product Listing Form states:

> *"Do not list clinical laboratory services as a product. We do not consider this to be blood product manufacturing. Record compatibility testing in the testing column for the appropriate product"*

Under process definitions, "Test" refers to product testing such as blood grouping, syphilis, hepatitis, HIV, and protein electrophoresis, as well as compatibility testing (crossmatching). It does not include daily quality control tests of reagents.

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FDA Registration – Product Listing *(cont'd)*

Question 18: If the blood establishment performs antibody screening on the donor sample retention tube and a positive result triggers the destruction of plasma and apheresis platelets, should "Test" (column 8) be marked for these products?

FDA/OBRR Response Q18:

"Yes. The type of testing referenced in this question is considered part of "compatibility testing". In this example, antibody screen testing is being performed on a Whole Blood donor sample, and not a sample from a separate plasma or platelet product. Therefore, 'Test' would need to be included as the process activity and 'Whole Blood' as the product."

FDA Registration – Product Listing *(cont'd)*

Question 19: If the blood establishment performs antibody titers on the unit to determine if the whole blood qualifies and is labeled as low titer O Whole Blood, should "Test" (column 8) be marked for whole blood?

FDA/OBRR Response Q19:

"No. Performing antibody titers **on a specific blood product** or donor sample is not an activity defined under the process definition "Test", and therefore would not need to be included on the establishment's Blood Establishment Registration."

Cont'd on following page

FDA Registration – Product Listing *(cont'd)*

Question 20: Would there be a different determination if the test was performed on the donor sample retention tube?

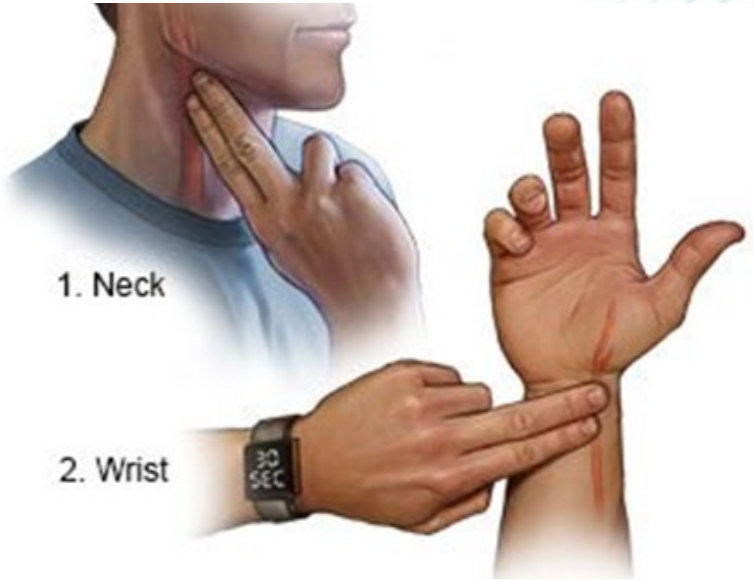
FDA/OBRR Response Q20:

"No, as explained in my previous response, performing antibody titers on a specific blood product **or donor sample** is not an activity defined under the process definition "Test"."

FDA Blood Pressure and Pulse Donor Eligibility Requirements – Compliance Policy

Background: The Blood Pressure and Pulse Donor Eligibility Requirements – Compliance Policy | FDA describes circumstances in which FDA does not intend to take regulatory action for a blood establishment's failure to comply with regulations for determining the eligibility of athletic blood donors with pulse rates below 50 bpm.

Question 21: Would the FDA approve submissions for donors with a high pulse?



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FDA Blood Pressure and Pulse Donor Eligibility Requirements – Compliance Policy *(cont'd)*

FDA/OBRR Response Q21:

"The guidance presents our current thinking, and we do not intend to approve submissions or extend the enforcement policy to donors with a high pulse. An elevated pulse before donation has been shown to be associated with increased risk of vasovagal reactions and such donors are typically deferred unless the responsible physician determines eligibility. Therefore, in accordance with 21 CFR 630.10(f)(4), for a donor with an elevated pulse, the responsible physician must determine and document at each donation, that the health of the donor would not be adversely affected by donating. This determination must not be delegated but may be performed by telephonic or other offsite consultation (21 CFR 630.5(b) and (c))."

Artificial Intelligence (AI)

Background: Our facility is considering the use of AI to interpret the standard operating procedures (SOPs) in our firm's document system to generate steps in a process based on the SOP language. For example, a user can access an AI feature and ask, "How do I perform a phlebotomy?". AI will then scan the firm's SOP data base/actual SOPs, synthesize the content, and then create the steps for the user to follow.

Question 22: What is FDA's current thinking on the use of AI for this purpose?

Cont'd on following page

Artificial Intelligence (AI) *(cont'd)*

FDA/OBRR Response Q22:

"We have some concerns about the use of AI as proposed in this scenario. However, while we have not issued specific recommendations for use of AI in blood establishments, we recognize that AI will eventually become part of how we live and work. FDA has released two discussion papers to spur conversation about artificial intelligence and machine learning in drug development and manufacturing. We expect to have further questions about how it could be used and validated as part of the development of SOPs that are reviewed by FDA or other evolving uses. As stated in the discussion paper, FDA is planning a workshop to discuss how the community can work together to realize the potential of AI for product development while being mindful of potential challenges.

Links to FDA's discussion papers are available on our website: https://www.fda.gov/news-events/fda-voices/fda-releases-two-discussion-papers-spur-conversation-about-artificial-intelligence-and-machine"

Labeling – Final Container Label

Background: 21 CFR 606.121 Container label states:

(b) The label provided by the collecting facility and the initial processing facility must not be removed, altered, or obscured, except that the label may be altered to indicate the proper name of the product, with any appropriate modifiers and attributes, and other information required to identify accurately the contents of a container after blood components considered finished products have been prepared."

Our facility would like to go to a full-face label for our ***final*** container label. The ***final*** label and donor identification number (DIN) will not be "removed, altered or obscured." The full-face label will merely cover the initial DIN placed on the bag by collections. The full-face label is a real time-saver, since initial DINS are inconsistently placed on the bag for the cut-out label.

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Labeling – Final Container Label *(cont'd)*

FOR AUDIENCE RESPONSE:

Question 23: Does this practice meet the requirements of 21 CFR 606.121?

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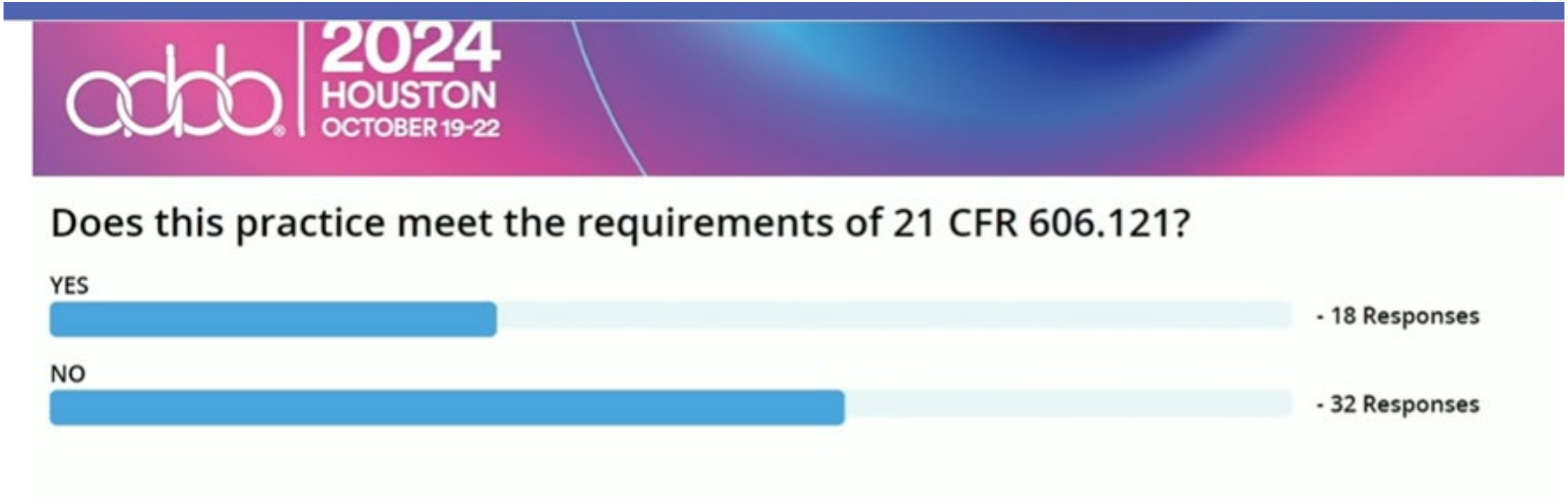
Labeling – Final Container Label *(cont'd)*

AUDIENCE RESPONSE:



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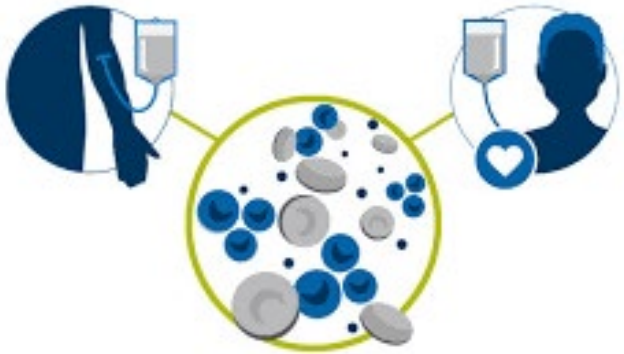
Labeling – Final Container Label *(cont'd)*

FDA/OBRR Response Q23:

"Yes. Per 21 CFR 606.121(b), the original blood component container label can be altered to indicate the proper name of the product with the appropriate product code and any modifiers, attributes and other information required to accurately identify the contents of the container after the final component has been prepared. You may apply a new full-face label if the Donation Identification Number (DIN) on the new label is the same as the DIN on the original label so that traceability of the component to the donor is maintained [21 CFR 606.121(c)(3)]."

ASK THE FDA

Cellular Therapy



Exceptions

Background: 21 CFR 1271.15(a) provides the following exception:

> *(a) You are not required to comply with the requirements of this part if you are an establishment that uses HCT/P's solely for nonclinical, scientific, or educational purposes.*

Question 1: Does the exception apply to certain parts of 21 CFR 1271 or to the entire 21 CFR 1271?

FDA/OTP Response to Q1:

"The exception for nonclinical, scientific, or educational purposes applies to the entirety of 21 CFR 1271."

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Exceptions *(cont'd)*

Question 2: Does the exception apply to all HCT/Ps that are for non-clinical, scientific, or educational purposes or is applicability only for HCT/Ps regulated solely under section 361 of the Public Health Service Act?

FDA/OTP Response to Q2:
"The exception applies to all HCT/Ps when the HCT/Ps are solely used for non-clinical studies or education purposes."

Collection of an Otherwise Deferred Donor – Disclosure of Information

Background: 21 CFR 1271.65(b)(1) provides the limited uses of an HCT/P product collected from a donor determined to be ineligible. Use is not prohibited under the following circumstances:

> *"(i) The HCT/P is for allogeneic use in a first-degree or second-degree blood relative;*
>
> *…*
>
> *(iii) There is a documented urgent medical need as defined in §1271.3(u)."*

And further provides:

> *"(2) You must prominently label an HCT/P made available for use under the provisions of paragraph (b)(1) of this section with the Biohazard legend shown in §1271.3(h) with the statement "WARNING: Advise patient of communicable disease risks," and, in the case of reactive test results, "WARNING: Reactive test results for (name of disease agent or disease)." The HCT/P must be accompanied by the records required under §1271.55."*

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Collection of an Otherwise Deferred Donor – Disclosure of Information *(cont'd)*

Question 3: When an HCT/P is collected from an ineligible donor who would otherwise be deferred for "at risk behavior" because they are the only available match and there is a documented urgent medical need what information must be disclosed to the recipient?

FDA/OTP Response to Q3:

"According to 21 CFR 1271.65(b)(i), an HCT/P from an ineligible donor is not prohibited from use for implantation, transplantation, infusion, or transfer of the HCT/P is for allogeneic use in a first-degree or second-degree blood relative, or if there is a documented urgent medical need as defined in 1271.3(u). The regulations in 21 CFR part 1271 specify the communicable disease risk be provided to the physician using the HCT/P. The establishment that manufactured the HCT/P from the ineligible donor used under 1271.65(b)(i) must document that the establishment notified the physician of the results of testing and screening in accordance with 1271.65(b)(iii).

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Collection of an Otherwise Deferred Donor – Disclosure of Information *(cont'd)*

FDA/OTP Response to Q3 (cont'd):

Under 1271.65(b)(ii), an HCT/P from an ineligible donor must also be prominently labeled with a biohazard legend with a statement warning "Advise patient of communicable disease risks" and indicates a reactive test results warning "Reactive test results for …" and then indicate the name of disease agent or disease. Additional labeling requirements can be found at 1271.370.

Furthermore, the HCT/P must be accompanied with the records required under 1271.55. In the case of an HCT/P from a donor who is ineligible based on screening and released under paragraph (b) of 1271.65, a statement noting the reason for determining ineligibility must be included.

The required labeling and accompanying records are to help ensure that physicians have specific and accurate information in weighing the risks and explaining the risks of using an HCT/P from an ineligible donor to the recipient, recognizing that physicians are under legal and ethical restrictions requiring them to discuss the risk of communicable disease transmission stemming from use of the HCT/P's."

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Collection of an Otherwise Deferred Donor – Disclosure of Information *(cont'd)*

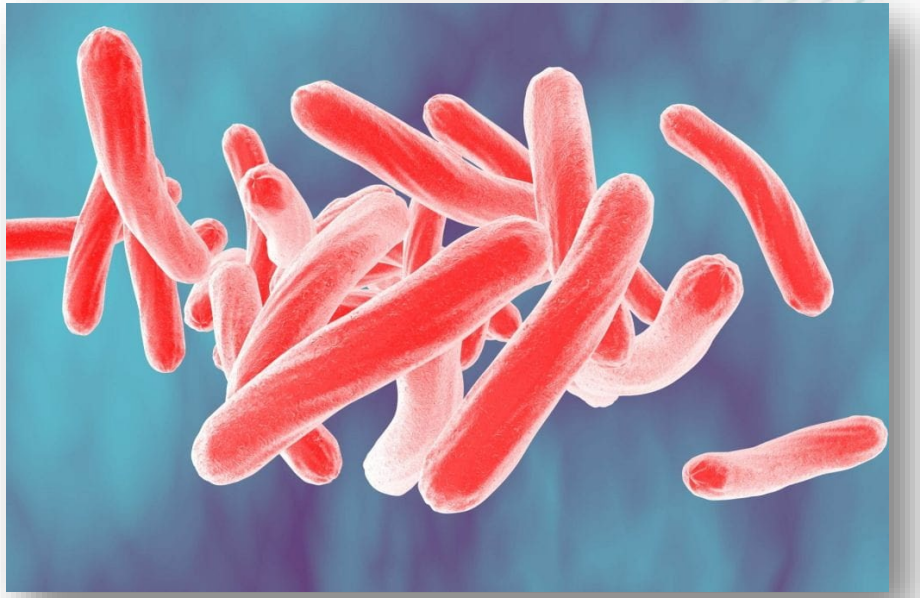
Question 4: When this donor is a first- or second-degree blood relative is there an obligation to protect the confidentiality of the donor's risk information and specific test results obtained during the screening process?

FDA/OTP Response to Q4:
"The labeling and accompanying records requirements described in response to the previous question are applicable to all donors of HCT/P's, including first- or second-degree blood relatives of HCT/P donors.

The accompanying records under 1271.55 require a distinct identification code affixed to the HCT/P container that relates the HCT/P to the donor and to all records pertaining to the HCT/P. The distinct identification code must not include an individual's name, social security number, or medical record number; however, an exception is provided for autologous donations, directive reproductive donations, or donations made by first-degree or second-degree blood relatives. This means the label of an HCT/P from a first-degree or second-degree blood relative donor may include a distinct identification code or the donor's name or other identifying information."

Mycobacterium tuberculosis (Mtb) in Bone Matrix

Background: Following the recent Mtb outbreak linked to a bone matrix product, FDA issued Important Information for HCT/P Establishments on 09/06/23 and a Bone Matrix Product: FDA Safety Communication on 09/23/24 which contained Risk Mitigation Strategies and considerations regarding the risk of transmission of Mtb through the use of HCT/Ps.



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Mycobacterium tuberculosis (Mtb) in Bone Matrix *(cont'd)*

Question 5: Is the intent of the recommendations in these communications to screen all HCT/P donors or only donors of HCT/Ps that could potentially transmit Mtb to recipients such as for example bone or bone marrow donors?

FDA/OTP Response to Q5:
"The considerations and risk mitigation strategies described in FDA safety communication '*Important Information for HCT/P Establishments*' published on September 6, 2023, and bone matrix product FDA safety communication published on September 12, 2023, apply to all HCT/P donors."

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Mycobacterium tuberculosis (Mtb) in Bone Matrix *(cont'd)*

Question 6: Should HCT/P donors with any risk of Mtb infection be considered ineligible, or is this determination left to the discretion of the authorized individual at the establishment responsible for determining donor eligibility?

FDA/OTP Response to Q6:
"Currently, *Mycobacterium tuberculosis* is not a relevant communicable disease agent or disease, and there are no requirements to screen or test donors of HCT/Ps for this infectious agent.

FDA provides risk mitigation strategies for screening donors of HCT/Ps for Mtb transmission risk. These risk mitigation strategies are not recommendations, guidance, or requirements. Routine screening measures are in place for evaluating clinical evidence of infection in HCT/P donors. FDA has provided recommendations and guidance to reduce the risk of transmission infections, including deep sepsis, which may be caused by Mtb. The HCT/P

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Mycobacterium tuberculosis (Mtb) in Bone Matrix *(cont'd)*

FDA/OTP Response to Q6 *(cont'd)*:

establishment's responsible person must determine and document the eligibility of a cell or tissue donor under 21 CFR 1271.50. The responsible person who is authorized to perform designated functions related to the donor eligibility determination should have appropriate medical training and be qualified to review clinical evidence consistent with the risk for sepsis and TB infections. In addition, according to 21 CFR part 1271.150, establishments must follow CGTP requirements to prevent the introduction, transmission, and spread of communicable disease by HCT/Ps, which includes ensuring that HCT/Ps do not contain communicable disease agents such as Mtb."

Conditioned Medium

Background: 21CFR1271.3 lists articles that are not considered HCT/Ps including the following:

"(3) Secreted or extracted human products, such as milk, collagen, and cell factors;…"

Conditioned medium is typically derived from HCT/Ps, such as adipose or cord tissue where the mesenchymal stem cells (MSCs) are isolated, cultured and the supernatant harvested as conditioned medium, either in whole or further separated for therapeutic use for variety of conditions.

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Conditioned Medium *(cont'd)*

Question 7: Per the regulation referenced, is conditioned medium considered an extracted human product and not an HCT/P?

FDA/OTP Response to Q7:
"Yes, conditioned medium derived from culturing cells is generally not considered a human cell, tissue, or cellular and tissue-based product or HCT/P because it is a secreted or extracted human product. Conditioned medium derived from human cells or tissues is regulated as a drug and biological product and subject to regulations under section 351(a) of the Public Health Service Act and the Food, Drug, and Cosmetic Act when the conditioned medium product is intended for therapeutic indications. However, conditioned medium intended for use as reagents for further manufacturing of other products are considered ancillary reagents and are not regulated separately from the finished product."

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Conditioned Medium *(cont'd)*

Question 8: If it is considered an extracted product, what is FDA's thinking on the applicable regulations for autologous and allogenic use?

FDA/OTP Response to Q8:
"We do not expect the applicable regulatory oversight for the final conditioned medium product to be any different between conditioned medium products intended for autologous or allogeneic therapeutic use. We generally recommend sponsors for conditioned medium products follow the procedures outlined in 21 CFR Part 1271 for donor eligibility."

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Conditioned Medium *(cont'd)*

Question 9: Would this product be regulated as a biologic, drug or both?

FDA/OTP: Response to Q9:
"Conditioned medium products that are derived from human cells or tissues and intended for therapeutic indications are regulated as drugs and biological products under section 351 of the PHS Act and the Food Drug and Cosmetics Act and are subject to pre-market review and approval requirements to lawfully market a drug that is also a biologic product, a valid biologics license must be in effect. Such licenses are issued only after a demonstration that the product is safe, pure, and potent. In investigational stage ID prior to approval of a biologics license for commercial distribution, such products may only be distributed to participating investigators and/or administered to humans if a sponsor has an investigational new drug application in effect as specified by FDA regulations 21 USC 355(i), 42 USC 262.(a)(3), and 21 CFR part 312."

MSCs and the Practice of Medicine

Background: In our practice we see the use of MSCs derived from all tissue types. They are used in orthopedic infusions, hair injections and other non-homologous uses of MSCs in plastic surgery such as breast augmentation and rejuvenation fillers. These products are used autologously with at times disastrous results.

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MSCs and the Practice of Medicine *(cont'd)*

Question 10: Is it considered the "practice of medicine" if the MSC is processed and cultured for a few days within the same surgical suite where surgery is performed?

FDA/OTR Response to Q10:

"We believe you may be referring to off-label use. Please be aware that off-label use is only applicable for approved or licensed products that are used by physicians in the treatment of a particular disease or condition for which the drug or biological product is not otherwise approved. Off-label use does not apply to unapproved products. Generally, cultured MSCs are regulated as drugs and biological products and regulated under the Federal Food, Drug, and Cosmetic Act and/or section 351 of the PHS Act. Please also be aware that cultured MSCs do not generally meet the same surgical procedure exception."

MSCs and the Practice of Medicine *(cont'd)*

Question 11: Do FDA regulations for HCT/Ps for nonhomologous use apply?

FDA/OTR Response to Q11:
"Yes. In order to determine how an MSC product is regulated, the criteria at 1271.10(a), including homologous use, would apply. However, please be aware that MSCs intended to treat, cure, prevent, or mitigate disease or conditions are generally regulated as drugs and biological products and generally not appropriately regulated solely under section 361 of the PHS Act."

Question 12: Does FDA plan to release guidance related to these types of uses of MSCs?

FDA/OTR Response to Q12:
"The FDA cannot comment on the release of any future Guidances under consideration."

Unapproved Stem Cell Therapies

Background: Some states have enacted laws that include requirements related to the use of stem cell therapies that are not approved by FDA. For example, in May 2024, Utah State enacted a law that includes, but is not limited to the following language:

> *"(2) A health care provider whose scope of practice includes the use of stem cell therapy may perform a stem cell therapy that is not approved by the United States Food and Drug Administration, if the health care provider provides the patient with the following written notice before performing the therapy:*
>
> *'THIS NOTICE MUST BE PROVIDED TO YOU UNDER UTAH LAW. This health care practitioner performs one or more stem cell therapies that have not yet been approved by the United States Food and Drug Administration. You are encouraged to consult with your primary care provider before undergoing a stem cell therapy.'"*

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Unapproved Stem Cell Therapies *(cont'd)*

Question 13: Would FDA comment on this practice and state policy?

FDA/OTR Response to Q13:

"This state legislation does not alter FDA authority to regulate stem cell products under the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act. FDA has posted the following resources for consumers and patients that discuss the potential risks and provides advice for people considering the use of these products, which include potential risks of treatment with unapproved regenerative medicine products, consumer alert on regenerative medicine products, including stem cells and exosomes, and advancing the development of safe and effective regenerative medicine products."

Reserve Samples

Background: 21 CFR 211.170(a) provides the requirements for retaining a reserve sample of an HCT/P regulated as a drug product:

> *"(1) For an active ingredient in a drug product…the reserve sample shall be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient."*

21 CFR 600.13 Retention samples requires:

> "*Manufacturers shall retain for a period of at least 6 months after the expiration date…of each lot of each product"*

21 CFR 1271 does not include requirements for retention of HCT/P sample after expiration, except for dura matter (21 CFR1271.290).

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Reserve Samples *(cont'd)*

Question 14: Which retention time is applicable if my HCT/P is regulated as a biologic and a drug?

FDA/OTR Response to Q14:

"For HCT/Ps regulated as a biologic and a drug, the samples should be retained for the longer duration, as stated in 21 CFR 211.170(a) for the availability of the reserve sample of the drug product containing the active ingredient."

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Reserve Samples *(cont'd)*

Question 15: Some competent authorities require retention of HCT/P donor plasma for future use in case of retrospective testing to confirm unknown pathogens/emerging ID testing. Could the FDA comment on this?

FDA/OTR Response to Q15:
"Per the definition in 21 CFR 1271(3)(d) human cells tissues and cellular- and tissue-based products HCT/P consist of human cells or tissues intended for implantation and transplantation, infusion or transfer into human recipient. Plasma is not considered an HCT/P, because it is a blood product. And for reference, you may see 21 CFR, 1271(3)(d)(ii) for products that meet the definition of an HCT/P and which are regulated solely under Section 361 of the Public Health Services Act. The regulations in 21 CFR Part 1271, do not include requirements for retaining samples or specimens from HCT/P donors or samples or finished products for future testing or other purposes, except for requirements specific to dura mater donors under 21 CFR 1271.290(g), we cannot comment on requirements from other competent authorities' auditing a manufacturing facility."

Auditing a Manufacturing Facility

Background: We are interested in partnering with a company in the US that has obtained an investigational new drug application (IND) for a cell and gene therapy (CGT) product. We are debating whether we should conduct our own audit of the company's manufacturing facility where the product under IND is manufactured or rely on the FDA process to ensure FDA regulations (in particular cGMP) are met.

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Auditing a Manufacturing Facility *(cont'd)*

Question 16: Can we assume that FDA has visited the drug manufacturing establishment before an IND approval (or soon after and IND is approved) to ensure that the FDA cGMP requirements are met?

FDA/OTP Response to Q16:

"So, for FDA response on that question, as a general matter, INDs are not approved by FDA. After submission, CBER will review the IND application to ensure compliance with regulatory requirements and assess the safety and scientific merit of the proposed clinical studies. The review process may include requests for additional information or clarification from the sponsor. After CBER reviews the IND application within 30 days from the receipt and notifies a sponsor that the study is safe to proceed, the sponsor can initiate the clinical study. If the study is deemed not safe to proceed due to deficiencies, the IND is subject to a clinical hold. For more information, you can see our website under INDs and there is a web address, but if you

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Auditing a Manufacturing Facility *(cont'd)*

FDA/OTP Response to Q16 *(cont'd)*:

go to our website and look up investigational new drug applications, you'll be able to find the information. FDA does not perform routine cGMP inspections of manufacturers of investigational new drugs prior to the IND going into effect. Nor does FDA perform routine cGMP inspections during the Clinical Investigation phases of the study. FDA Buyer Research Monitoring Program is a comprehensive program of on-site inspections, data audits, and remote regulatory assessments designed to monitor all aspects of the conduct and reporting of FDA regulated research. The program is established to assure the quality and integrity of data submitted to the Agency in support of new product approvals and marketing applications, as well as to provide protection of the rights and welfare of the thousands of human subjects and animals involved in FDA regulated research."

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Auditing a Manufacturing Facility *(cont'd)*

Question 17: Are there times when FDA approves the NDA for a CGT product without visiting the drug manufacturing establishment? A brief overview of this process would be greatly appreciated.

FDA/OTP Response to Q17:

"FDA regulates cellular therapy products and human gene therapy products under both the Public Health Service Act and the Federal Food and Drug and Cosmetic Act as enabling statutes for oversight. Cellular therapy products include cellular immunotherapies, cancer vaccines, and other types of both autologous and allogeneic cells for certain therapeutic indications, including hematopoietic stem cells and adult and embryonic stem cells. Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. CBER has approved both cellular and gene

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Auditing a Manufacturing Facility *(cont'd)*

FDA/OTP Response to Q17 *(cont'd)*:

therapy products using the biologics license application pathway, not the NDA pathway. A list of these products may be found on the approved cellular and gene therapy products web page. Section 351 of the Public Health Service Act and Section 704 of the Federal Food, Drug and Cosmetic Act provide the regulatory authority to conduct inspections at any establishment where biological products are manufactured under 21 CFR 601.20: "…*A biologics license shall not be issued except under upon a determination that the product and establishment comply with the applicable regulations under the reauthorization of the prescription drug user fees in the Food and Drug Administration Modernization Act of 1997...*" An inspection, if needed, is considered to be part of the complete review of an application. A pre-license inspection or pre-approval inspection is performed at establishments named in the biologics license application or BLA or supplement to ensure compliance with applicable requirements and to assure that the data submitted are accurate and complete. CBERs policy is to ensure that manufacturing

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Auditing a Manufacturing Facility *(cont'd)*

FDA/OTP Response to Q17 *(cont'd)*:

establishments and processes meet the appropriate requirements and comply with the regulations through inspections and review; CBER will determine if a PLI or PAI is necessary based on CBERs SOP P8410 determining when pre-license or pre-approved approval inspections are necessary, and more information on that SOP can be found on our website."

Cellular Starting Material - Listing

Background: 21 CFR 1271(b)(2) describes registration and listing requirements:

> *(b) "If you are an establishment that manufactures HCT/P's that are regulated as drugs, devices and/or biological products under section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act, §§207.9(a)(5) and 807.20(d) of this chapter require you to register and list your HCT/P's following the procedures in part 207 (if a drug and/or biological product) of this chapter…"*

Our establishment performs cryopreservation of starting apheresis cell products (for example, MNC, A) that are shipped to another manufacturer and are subsequently manufactured into CAR-T products.

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Cellular Starting Material – Listing *(cont'd)*

Question 18: Which facility is required to list the product on the establishment registration?

Question 19: What are the elements to consider when determining whether an establishment is required to list cellular therapy starting material products on the establishment registration?

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Cellular Starting Material – Listing *(cont'd)*

FDA/OTP Response to Q18 & Q19 Combined:

"So, questions 18 and 19 both appear to be related to establishments that ship the starting cell product to another establishment for manufacture of HCT/Ps that are regulated as biological products, such as CAR-T cell products. Under 21 CFR 1271.1(b)(ii), an establishment that manufactures HCT/Ps that are regulated as drugs, devices, or biological products under Section 351 of the PHS Act and/or the Federal Food, Drug and Cosmetic Act, must register and list their HCT/Ps following the procedures in 21 CFR Part 207 or 807 as applicable, rather than 21 CFR Part 1271, FDA does not require establishments that manufacture HCT/Ps, regulated as drugs, devices and / or biological products that are the subject of an investigational new drug application or an investigational device exemption to register and list those HCT/Ps in accordance with 21 CFR Part 207 or 807 until the products receive marketing authorization. This is described on our tissue establishment registration website for drugs and or biological products. 21 CFR 207.13 provides a list of exemptions from the registration and listing requirements if your facility collects and/or cryopreserves a starting cell product. For manufacturers of a licensed biological product, you may contact the license holder of the product regarding any registration requirements they may be applicable to your facility. The license holder may contact the regulatory project manager assigned to their application if they have any questions."

HCT/P West Nile Virus Testing

Background: The Sep 2016 (corrected May 2017) HCT/P West Nile Virus Testing Guidance recommends performing individual donor NAT WNV testing on living donors of HCT/Ps recovered from Jun 1st through Oct 31st every year.

The 2009 Guidance for WNV Testing of Whole Blood and Blood Components recommends year-round testing by minipool NAT with switching to individual donor NAT during high WNV activity in the geographic area of collection.

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HCT/P West Nile Virus Testing *(cont'd)*

Question 20: Why are the HCT/P recommendations for testing different from the blood recommendations?

FDA/OTP Response to Q20:

"Based on data and available information, the recommended seasonal testing for living donors of HCT/Ps is appropriate to reduce the risk of transmission of West Nile virus. In addition, you must test using appropriate FDA licensed, approved, or clear donor screening tests in accordance with the manufacturer's instructions. According to the manufacturer's instructions for currently available donor screening tests for West Nile virus, mini pool NAT may only be used for screening donors of a whole blood and blood components for transmit transfusion for all other donors, specimens may only be screened as individual specimens or individual NAT. West Nile virus became endemic in the United States with higher viral activity during the warmer

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HCT/P West Nile Virus Testing *(cont'd)*

FDA/OTP Response to Q20 *(cont'd)*:

months of the year, which means the HCT/P donor population has a higher risk of becoming infected with West Nile virus during these months. For living donors of HCT/P, in an effort to identify the months during which the risk of infection is greatest, FDA CBER's Office of Biostatistics and Epidemiology performed an analysis of the data collected by AR Burnett from 1999 to 2013 as provided by the CDC. This was done to assess the seasonal and geographic patterns of West Nile virus infections in the United States. Analysis of this data indicates that greater than 98.5% of West Nile virus infections in each region of the United States occur between June 1 and August 31. The data also indicates that the pattern of seasonal activity has been consistent since the appearance of West Nile virus in the United States. Publicly available data that support this observation is maintained by the CDC."

Communicating with the Office of Therapeutic Products (OTP)

Background: The Office of Blood Research and Review, Blood and Plasma Branch, offers a very helpful email address to submit inquiries. (CBEROBRRBPBInquiries@fda.hhs.gov). The questions are then forwarded to the appropriate FDA staff for response. With the creation of the new Super Office, OTP, it is sometimes difficult to know how and where to submit biotherapy questions.

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Communicating with the Office of Therapeutic Products (OTP) *(cont'd)*

Question 21: Is OTP considering the creation of an email similar to the OBRR email to handle questions?

FDA/OTP Response to Q21:
"This is a good question. Manufacturers may submit inquiries for OTP to industry.biologics@FDA.hhs.gov where questions are forwarded to the appropriate FDA staff within OTP for a response for product development questions. You may refer to our website under interactions with Office of Therapeutic Products for ways to informally and formally interact with OTP."

Ask CMS/CLIA

CD34+ Counts – Peripheral Blood

Background: When performing a peripheral blood stem cell collection, various clinical protocols and physicians have differing requirements for the target CD34+ dose needed to proceed to transplant. Testing CD34+ cell count in peripheral blood before collection provides the collection staff and physicians knowledge on what to expect from the peripheral blood stem cell product. This knowledge can be used to determine if multiple collections may be needed.

Question 1: Does CLIA believe this testing falls underneath their purview?

CMS Response Q1:
"Yes, this test falls under the purview of CLIA as it is testing on a patient/donor and not the product. 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."

CLIA – Laboratory Director Responsibilities

Background: The August 2016 CLIA Laboratory Directory Responsibilities brochure, page 2 states:

"As laboratory director, you must ensure that:

…

- *sufficient numbers of appropriately educated, experienced, and/or trained personnel who provide appropriate consultation, properly supervise, and accurately perform tests and report test results in accordance with the written duties and responsibilities specified by you, are employed by the laboratory;"*

This is identified as a task which cannot be delegated.

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CLIA – Laboratory Director Responsibilities *(cont'd)*

Question 2: Is the laboratory director responsible for reviewing and signing the verification of the experience and education qualifications of testing personnel and CLIA designees?

CMS Response Q2:

"The CLIA laboratory director is ultimately responsible for ensuring that testing personnel meet the required educational and experience qualifications. The task of reviewing and signing the verification of experience and educational qualifications of testing personnel may not be delegated."

CLIA – Laboratory Director Responsibilities *(cont'd)*

Question 3: If "Yes," is the expected timeframe for those verifications to occur at the time of employee hire or role change, or can it be done for example, as a quarterly review of all new staff in the quarter?

CMS Response Q3:
"Verification should occur at the time of hire or role change."

Review of Laboratory Information System (LIS) Procedures

Background: 42 CFR 493.1251 Standard: Procedure Manual states:

> *"(d) Procedures and changes in procedures must be approved, signed, and dated by the current laboratory director before use."*

Question 4: Can the review of LIS procedures related to computer, facility, system maintenance and security, reporting of results be delegated?

CMS Response Q4:
"This duty cannot be delegated."

Applicability of CLIA Regulations – Titer Testing

Background: After blood products are manufactured, our blood center randomly selects Plasma and Apheresis Platelet components and performs anti-A or anti-B titers using the donor samples. This testing allows our establishment to provide low-titer blood components to hospitals.

Question 5: Do CLIA regulations apply to the testing used to determine these titers?

CMS Response Q5:

"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

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Applicability of CLIA Regulations – Titer Testing *(cont'd)*

CMS Response to Q5 *(cont'd)*:

antibodies. CMS considers the intended purpose of this test as 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."

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Questions?

Ask the FDA and CLIA Transcripts

Thank you!

Contact AABB's Regulatory Affairs Staff at

regulatory@aabb.org