



Ask the FDA and CMS/CLIA

2019 AABB Annual Meeting
San Antonio, Texas

Oct. 21, 2019

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:

- **Sharon Carayiannis, MT(ASCP)HP**

Deputy Director

- **Karen Palmer, MT(ASCP) CQA(ASQ)**

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Objectives

- Apply a regulatory strategy for regulations recently issued by the Food and Drug Administration (FDA).
- Apply FDA's recommendations in recently issued guidance to industry.
- Describe FDA's approach for blood and human cell, tissue, and cellular and tissue-based products (HCT/Ps) policies, regulations and inspection programs.

Thank you

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

We also appreciate the support of both the FDA and the Centers for Medicare & Medicaid Services (CMS).

Our FDA Attendees:

Anne Eder, MD, PhD, Deputy Director, CBER/OBRR

Carlos Villa, MD, PhD, Medical Officer, OBRR/DBCD

Judy Ellen Ciaraldi, BS, MT(ASCP)SBB, CQA(ASQ), Consumer Safety Officer (CSO), DBCD

Miriam Montes, MS, MT(ASCP)SBB, CSO, DBCD/BPB

Sharon O'Callaghan, CSO, OBRR/DIS

Tricia Martinez, Director, ORA, OPBO/Investigations Branch

Hanh Khuu, MD, Physician, CBER/OTAT/DHT/HTRB

Our CMS Attendee:

- Mary Hasan, MPA, BS, MT(ASCP), Clinical Laboratory Scientist

And thank you to Daralyn Hassan and Jelani Sanaa for collaborating on the CMS responses

You can find these slides with responses to your questions on the AABB website!

The screenshot shows a web browser window displaying the AABB website. The address bar shows the URL: <http://www.aabb.org/advocacy/regulatorygovernment/Pages/RegulatoryAffairs>. The page features a navigation menu with categories like STANDARDS & ACCREDITATION, PROGRAMS & SERVICES, ADVOCACY, PROFESSIONAL DEVELOPMENT, RESEARCH, and MEMBERSHIP. The main content area is titled "Regulatory Affairs" and includes a sidebar with various topics such as "Biologics License Applications", "Blood and Blood Components", and "HIV". The main text discusses federal regulations and provides links to "Recent Actions" and "AABB Quick Links". A right-hand sidebar contains "AABB Quick Links" and "External Resources".

Home > Advocacy > Regulatory Affairs

Regulatory Affairs

This page includes information on federal regulations and recommendations, compliance issues, emerging risks, and donor and patient health and safety issues facing the transfusion medicine and cellular therapies communities. For more information and recent actions, select links to areas of interest below. In addition we recommend you refer to the **Recent Actions** and the **AABB Quick Links** for analyses and related resources that provide a more in-depth look at the subject matter and offer strategies for compliance.

AABB represents the interests of AABB members, donors, and patients in need of lifesaving blood and cellular therapy products through interactions with the FDA and other government agencies. The Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) has regulatory oversight of the blood and blood components used for transfusion or for further manufacture of pharmaceuticals, such as clotting factors, and products standards; related products, such as cell separation devices and blood collection and storage containers; infectious disease tests that help protect the safety of the blood supply; and products and devices supporting activities in transfusion services.

CBER also has regulatory oversight of cellular therapy products. CBER's authority to regulate these products follows several pathways, based on the product's processing, intended use, country of collection and manufacture, as described in detail on the [Cellular Therapies](#) pages.

AABB Quick Links

- [Analysis/Summary](#)
- [Comments](#)
- [Correspondence](#)
- [Statements](#)
- [FDA Guidances](#)
- [Regulatory and Public Meetings](#)
- [FDA Liaison Meetings](#)
- [May 2015 Final Rule Resources](#)
- [Ask the FDA and CLIA Transcripts](#)
- [Contact AABB's Public Policy Department](#)
- [Contact AABB's Regulatory Affairs Department](#)

External Resources

- [Health and Human Services](#)
- [Centers for Medicare and Medicaid Services](#)
- [Centers for Disease Control and](#)

**Watch for Regulatory Updates
EVERY FRIDAY!!**

We will notify you when the slides and responses are posted.



AABB Introduction [slides 1-8]

Sharon Carayiannis:

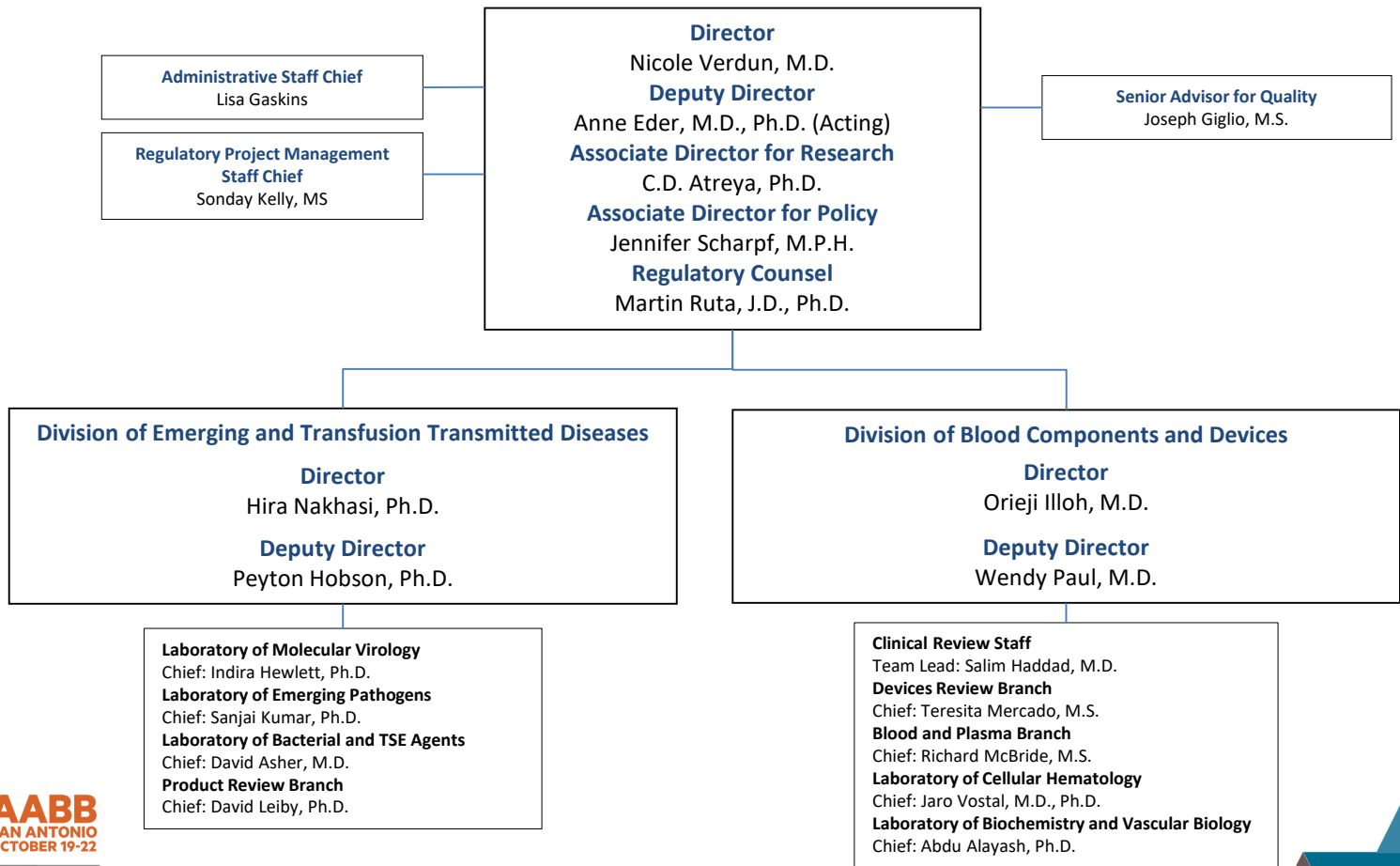
“Welcome to AABB’s 2019 Ask the FDA, CMS, and Clinical Laboratory Improvement Amendments (CLIA) Session. We’re always happy to see so many people in the audience, and today we have a livestream audience who we’re very excited to have join us in San Antonio. Thank you all for coming. Karen and I have no disclosures.

Our objectives today are to apply a regulatory strategy for regulations recently released, as well as for recommendations from FDA to describe FDA's approach for blood and human cell and tissue and cellular and tissue-based products, policies, regulations, and inspection programs. We want to start by thanking everyone. First, thank you to our members for always supporting this session and for the questions that you submitted. We also want to thank both FDA and CMS. They spend a lot of time developing responses to your questions and we're always appreciative of that. Today from FDA in the Office of Blood Research and Review (OBRR), we have Anne Eder, Carlos Villa, Judy Ciaraldi, and Miriam Montes. We also have Sharon O'Callaghan from the Office of Compliance and Biologics Quality, Tricia Martinez from Office of Biological Products Operations (OBPO), and Hanh Khuu from the Office of Tissues and Advanced Therapies.

We also have an attendee for CMS this year, Mary Hasan, and we want to also thank Daralyn Hassan and Jelani Sanaa for collaborating on the CMS responses. You'll be able to find these slides with responses added on the Regulatory section of AABB's website. Be sure to watch AABB Weekly Report for regulatory updates. That's where we'll announce when we have completed those slides and posted them. Now I'll invite FDA to provide an update.”

FDA: Update

Office Blood Research and Review : Organizational Chart



FDA Updates

- Blood Products Advisory Committee (BPAC) Update
 - Cold Stored Platelets
- Concurrent plasma for further manufacture
- Guidance updates
 - Bacterial Risk Control Strategies
- *Acinetobacter sp.* contaminated apheresis platelet investigation

BPAC – Cold Stored Platelets, Nov 22



Federal Register / Vol. 84, No. 191 / Wednesday, October 2, 2019 / Notices

52513

- The committee will discuss scientific considerations for cold stored platelet products intended for transfusion. The meeting will be open to the public.

<https://www.federalregister.gov/documents/2019/10/02/2019-21399/blood-products-advisory-committee-notice-of-meeting>

Guidance Updates – Recently Released

- *Further Testing of Donations that are Reactive on a Licensed Donor Screening Test for Antibodies to **Hepatitis C Virus**; Guidance for Industry (Oct 2019)*
- ***Bacterial Risk Control Strategies** for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion; Guidance for Industry (Sept 2019)*
- *Recommendations for Reducing the Risk of Transfusion-Transmitted **Babesiosis**; Guidance for Industry (May 2019)*
- *Testing for **Biotin** Interference in In Vitro Diagnostic Devices; Draft Guidance for Industry (June 2019)*

Guidance Agenda for 2019

- *Use of Serological Tests to Reduce the Risk of Transfusion-Transmitted Human T Lymphotropic Virus Types I and II (HTLV-I/II), Guidance for Industry*
- *Considerations for the Development of **Dried Plasma Products** Intended for Transfusion; Guidance for Industry*
- ***Implementation of Pathogen Reduction** Technology in the Manufacture of Blood Components in Blood Establishments: Questions and Answers; Guidance for Industry*
- *Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt Jakob Disease (**CJD**) and Variant Creutzfeldt-Jakob Disease (**vCJD**) by Blood and Blood Products; Draft Guidance for Industry*

FDA Introduction [slides 11-15]

Dr. Anne Eder:

“Good morning and thank you all for coming. Thanks to AABB for letting us have these sessions, and thanks also to those of you who attended our Center for Biologics Evaluation and Research (CBER) session yesterday. I’m going to make just a few introductory comments about what’s new in OBRR and give a brief update before we get to the questions.

There have been some changes in our leadership team. The Organization of OBRR is shown on this slide. Our Office Director is Dr. Nicole Verdun, who unfortunately cannot be at AABB today because of a conflict. I’m the Deputy Director in OBRR, and our divisional leadership is here as well. We have two divisions, the Division of Emerging and Transfusion Transmitted Diseases, led by Dr. Hira Nakhasi and Dr. Peyton Hobson, and the Division of Blood Components and Devices, led by Director Dr. Oriji Illoh, and Deputy Director Dr. Wendy Paul. Both Dr. Illoh and Dr. Paul are here at AABB. I also want to recognize Rick McBride, our Blood and Plasma Branch chief, and several of our consumer safety officers (CSO) that are here today. I want to recognize them for their dedication and service.

FDA Introduction [slides 11-15] (cont'd)

We have a few updates. Operationally, we've been looking at how we manage our workload and how we can more effectively and efficiently work in teams, so we can provide you with complete and consistent responses as promptly as possible. Our intent is that this effort is seamless, and we've already begun, but we will be communicating probably in the next six months about the changes and how we work in teams.

A question came up yesterday about two recent executive orders that some of you have been asking about. They are two executive orders on promoting the rule of law through improved guidance documents. The question of course was, 'How will this affect us?'. Our response is that once fully implemented, we will have a better understanding of any implications, but at this time we do not expect and have not made any changes to our guidance agenda, which I'll show you. There was also a question in this session, a perennial question, about concurrent plasma for further manufacture. We are still working toward finding a regulatory path forward. Our goal is to ensure that the approach meets the needs of our industry, maximizes each donation and reduces waste of plasma. Finally, we are trying something new. We will have five audience participation questions. So, this is 'Ask the FDA', but today we will be asking you what you think the answer is, or maybe what you want the answer to be. Either way is fine, and then we will answer it.

FDA Introduction [slides 11-15] (cont'd)

A few brief updates on the BPAC. I have already mentioned concurrent plasma. Dr. Carlos Villa will also give an update on the bacterial risk guidance that was released, and then an investigation into apheresis platelets contaminated with *Acinetobacter sp.* Our BPAC is meeting on Nov. 22, 2019 to discuss cold stored platelets, and the committee will discuss scientific considerations for cold stored platelet products intended for transfusion. The meeting is open to the public. These are the guidances that have been recently released: further testing of donations that are reactive on a screening test for hepatitis C virus; the bacterial risk control strategy guidance, which Dr. Villa is going to give us an update on; and the recommendations for reducing the risk of transfusion-transmitted Babesiosis. We have a few questions in the session on that guidance.

This is our guidance agenda for 2019 and guidances we intend to release before the end of this year. This includes a guidance to reduce the risk of Human T-lymphotropic virus, considerations for the development of dried plasma products, implementation of pathogen reduction, and revised preventive measures to reduce the possible risk of transmission of CJD and vCJD by blood and blood products. Now I'd like to introduce Dr. Carlos Villa to give an update on the bacterial risk control strategy guidance.”

Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion; Guidance for Industry

Apheresis platelets

- 5 days
 - Large volume delayed sampling (LVDS) \geq 36 hours
 - Pathogen reduction
 - Primary culture \geq 24 hours + secondary culture \geq day 3
 - Primary culture \geq 24 hours + secondary rapid testing

Apheresis platelets

- Up to 7 days
 - LVDS \geq 48 hours
 - LVDS \geq 36 hours + secondary culture \geq day 4
 - LVDS \geq 36 hours + secondary rapid testing
 - Primary culture \geq 24 hours + secondary culture \geq day 4
 - Primary culture \geq 24 hours + secondary rapid testing

Pre-storage pools of Whole Blood Derived (WBD) platelets

- 5 days
 - LVDS \geq 36 hours
 - Primary culture \geq 24 hours + secondary culture \geq day 3
 - Primary culture \geq 24 hours + secondary rapid testing

Single units of WBD platelets

- 5 days
 - Rapid testing
 - Primary culture \geq 24 hours
 - Primary culture \geq 36 hours

Post-storage pools of WBD platelets

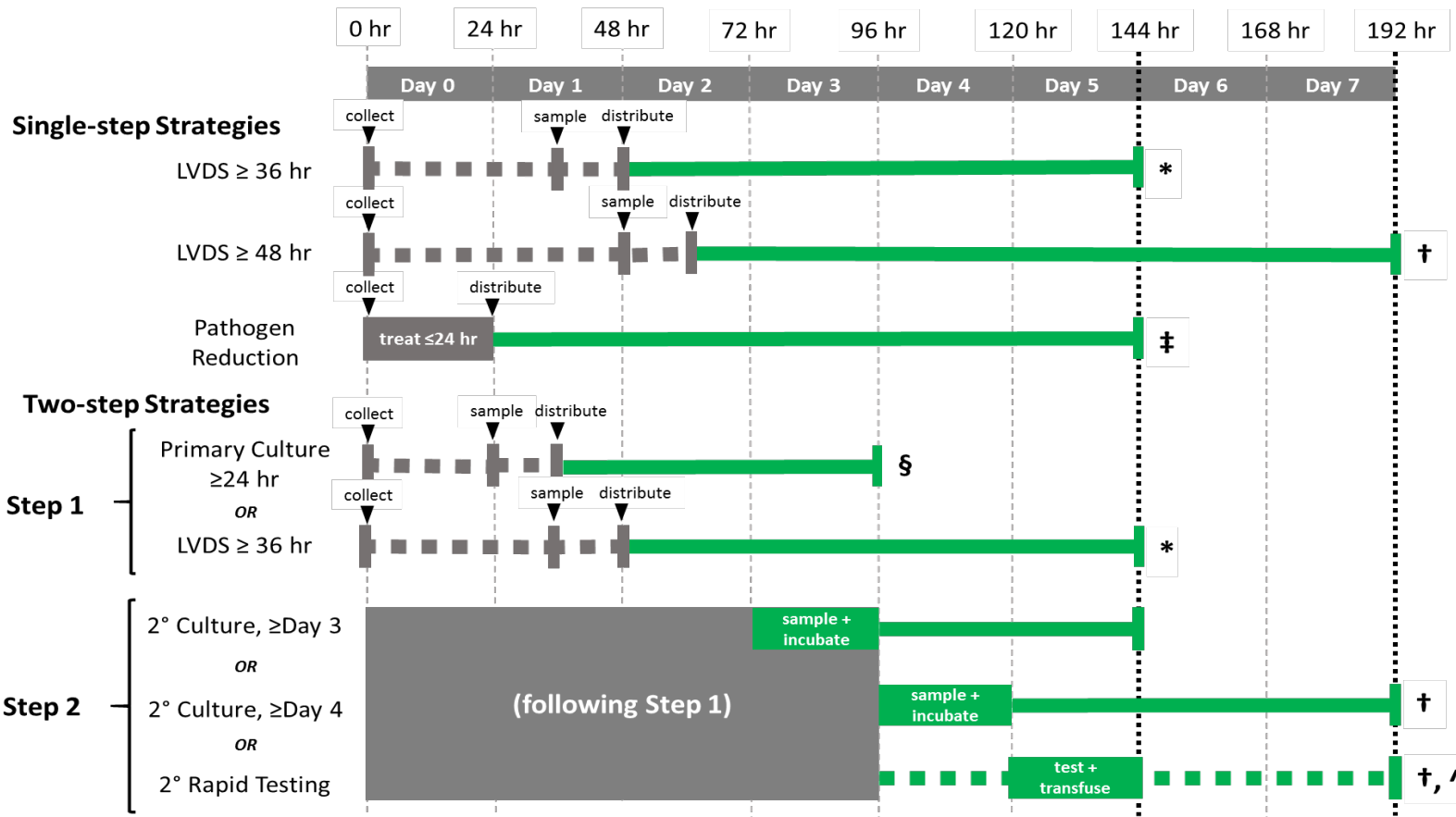
- 5 days
 - Rapid testing

Apheresis and pre-storage pools

Strategy	Applicable Components ¹	Time Performed	Volume Sampled ²	Product to be Sampled	Growth Conditions	Recommended Incubation Period	Expiry	
Single-step Strategies								
LVDS ≥36 hours	Apheresis and pre-storage pools	No sooner than 36 hours from the time of collection	≥16 mL total	Each apheresis split unit or pre-storage pool	Aerobic and anaerobic	Minimum of 12 hours	Day 5 ³	
LVDS ≥48 hours	Apheresis	No sooner than 48 hours from the time of collection	≥16 mL total	Each apheresis split unit	Aerobic and anaerobic	Minimum of 12 hours	Day 7 ⁴	
Pathogen Reduction	Per device instructions for use	Per device instructions for use	N/A	Per device instructions for use	N/A	N/A	Per device instructions for use	
Two-step Strategies								
Step 1	Primary culture ≥24 hours or LVDS ≥36 hours	Apheresis and pre-storage pools	No sooner than 24 hours from time of collection	≥ 16 mL total	Main collection (“mother bag”), each apheresis split unit, or pre-storage pool	Aerobic and anaerobic	Minimum of 12 hours	See note ⁵
		Apheresis and pre-storage pools	No sooner than 36 hours from the time of collection	≥16 mL total	Each apheresis split unit or pre-storage pool	Aerobic and anaerobic	Minimum of 12 hours	Day 5 ⁶
Step 2	Secondary culture	Apheresis and pre-storage pools	No sooner than day 3	≥8 mL	Each split unit or pre-storage pool	At least aerobic	Establish a minimum incubation time period in SOPs	Day 5
		Apheresis	No sooner than day 4	≥16mL total	Each split unit	Aerobic and anaerobic	Minimum of 12 hours	Day 7 ⁷
	Secondary rapid testing	Apheresis and pre-storage pools	Per device instructions for use	Per device instructions for use	Each apheresis split unit or pre-storage pool	N/A	N/A	Per device instructions for use (up to day 7 ⁸)

WBD single units and post-storage pools

Strategy	Applicable Components	Time Performed	Volume Sampled	Growth Conditions	Recommended Incubation Period	Expiry
Single-step Strategies						
Rapid testing	Single unit or post-storage pool	Per device instructions for use	Per device instructions for use	N/A	N/A	Per device instructions for use (up to day 5) ¹
Single culture	Single unit	No sooner than 36 hours from time of collection or No sooner than 24 hours from time of collection	Largest practical volume within the range permitted by the device instructions for use	At least aerobic	Minimum of 12 hours	Day 5 ²



Bacterial Risk Control Strategy Guidance FDA Commentary [slides 19-27]

Dr. Carlos Villa:

“Thank you everyone for coming today. We appreciate the opportunity to share this update with you. I will be providing a brief overview of the guidance. In the interest of time, I can't go into all the details of the guidance. On Sept. 30, 2019, FDA issued the final guidance document [*Bacterial Risk Control Strategies for Blood Collection Establishments in Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion*](#).

The final guidance provides recommendations to control the risk of bacterial contamination for platelets using a number of strategies that the user can choose from. FDA has established regulations to address the control of bacterial contamination of platelets. Under [*21 CFR 606.145\(a\)*](#), blood establishments and transfusion services must assure that the risk of bacterial contamination of platelets is adequately controlled using FDA approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose by FDA.

As the AABB Community is aware, the risk of bacterial sepsis due to contamination of platelet products stored at room temperature has persisted, despite the availability of interventions and bacterial detection methods that are widely used to test platelets today, prior to their release for transfusion.

Bacterial Risk Control Strategy Guidance FDA Commentary [slides 19-27] (cont'd)

Addressing this issue has been a high priority for the agency. Prior to issuing the final guidance document, FDA sought advice from BPAC and reviewed public comments to draft guidance documents. In response, the final guidance incorporates some of the following changes. The strategies for platelets have been outlined as either single-step or two-step, and I'll outline some of these strategies in a few slides in a moment.

LVDS no sooner than 36 hours has been added as an option and may be implemented with currently available devices. The addition of LVDS no sooner than 36 hours provides blood establishments and transfusion services an option that allows them to maintain a one-time testing model for 5-day storage while enhancing bacterial safety compared to current practices.

Additional changes including labeling, dating periods, inventory management, sampling procedures, and culture incubation periods have been clarified. This includes that following secondary testing, it is not expected that blood collection establishments or transfusion services retest units to determine platelet yield. Additionally, products may be shipped during the recommended culture incubation periods provided the blood culture establishment establishes procedures to maintain control of the products during the incubation period.

Bacterial Risk Control Strategy Guidance FDA Commentary [slides 19-27] (cont'd)

Additional recommendations for WBD platelets have been revised and clarified, and the recommended time frame for implementation of the recommendations by blood establishments and transfusion services has been extended to 18 months based on public comment. In addition, we've provided a series of new appendices, including tables and graphical timelines to clarify the available strategies and simplify and consolidate the recommendations.

I'll now briefly provide and review the available strategies in the associated tables and figures, including some of those appendices, for everyone to be aware of what strategies are available. For apheresis for five days, strategies include LVDS no sooner than 36 hours, pathogen reduction, and in two-step methods, primary culture no sooner than 24 hours followed by either secondary culture or secondary rapid testing. For storage of up to seven days, LVDS no sooner than 48 hours, as well as several two-step methods are outlined there. I won't go over the considerations in detail. Pre-storage pools of platelets includes several strategies for 5-day storage and single units of WBD platelets also includes several strategies for 5-day platelets.

Bacterial Risk Control Strategy Guidance FDA Commentary [slides 19-27] (cont'd)

Finally, there are strategies for post-storage pools of WBD platelets. I want to highlight some of the appendices and new tables in the guidance document. In this table we have consolidated the considerations for each of these strategies, including applicable components, time performed, volume sampled, product to be sampled, growth conditions for culture-based techniques, recommended incubation periods as applicable, and expiration dating. Hopefully this provides the community with a simplified, consolidated way to compare and understand these approaches. Similarly, for WBD single units and post-storage pools we've added a similar table. I encourage you to go to these tables, read through the details of these tables, and then refer back to the guidance text to understand each of these strategies.

Finally, we've also provided a figure that outlines the timelines for each of these strategies, that helps you to understand when each step should occur in the process, and some of the operational considerations for each of these strategies. Thank you very much, and I want to thank the public for their comments for these guidance documents. We looked at all these comments, we considered all these comments and they were important in helping us improve the recommendations in these guidances.”

Ask the FDA

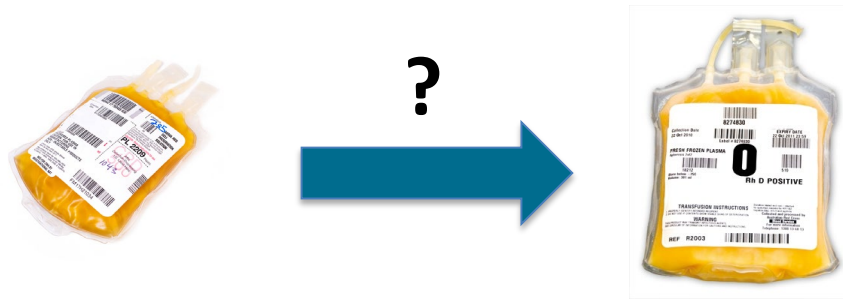
Blood and Blood Components

Recovered Plasma

Background: Many blood collection establishments routinely divert plasma produced in excess of transfusion needs into Recovered Plasma to fulfill a short-supply contract. These Recovered Plasma products have been separated, stored and tested in the same manner as plasma products for transfusion.

Question:

1) Can a product which has been labeled as Recovered Plasma be converted and relabeled to a transfusable plasma, such as fresh frozen plasma (FFP), provided it meets all of the safety, purity and potency requirements of FFP?



Recovered Plasma (cont'd)

FDA Response to Question 1: “The answer to the question is yes. However, this should not be performed as part of your routine procedures and practices, and more of an exception when you're facing inventory shortages. We do understand that sometimes that can be challenging. Yes, you can convert a product and relabel as plasma for transfusion provided the following: that the manufacturing of the products meets our product requirements (in [21 CFR 640.34](#), you will find the specifications for plasma processing of the various types of plasma); that you have records showing that the Recovered Plasma was manufactured in accordance with the regulations; that you have adequate procedures and quality measures in place to include defining the selection criteria for the units that will be converted; that you have a process that includes safeguards to avoid mix-ups when labeling these units (this is stated in [21 CFR 606.120\(a\)](#)); and finally that you follow the labeling regulations in [21 CFR 606.121](#).”

Plasma from a PAS Platelet and Donor Deferral

Background: Feedback from our membership reflects differing views on the apheresis collection of platelets with further manufacture into a Platelet Additive Solution (PAS) platelet and a plasma product.

Some collection facilities consider the plasma from a PAS platelet to be a concurrently collected plasma product which would affect donor deferral unless the facility has an alternate procedure approval under [§640.120](#) (also known as a variance). Others believe the deferral is based only on the collection of a platelet component and would not require a longer deferral based on the plasma collected during the platelet apheresis and removed as part of the PAS process.

Questions:

- 2) Is the plasma separated during the collection of a PAS platelet considered to be a concurrent plasma?
- 3) Is a variance approval required to defer the donor as a platelet donor rather than as a plasma donor?

Plasma from a PAS Platelet and Donor Deferral (cont'd)

Audience Response System (ARS) Response to Question 3:

Is a variance approval required to defer the donor as a platelet donor rather than as a plasma donor?

Yes



No



Plasma from a PAS Platelet and Donor Deferral (cont'd)

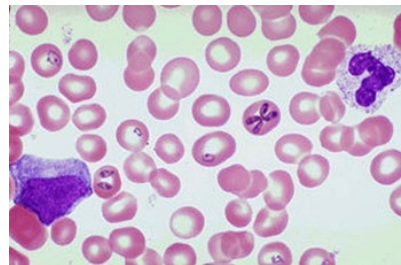
FDA Response to Questions 2 and 3: “The answer is no. The term ‘concurrent components’, also known as ‘co-components’, refers to separate components collected during the same plateletpheresis procedure or the red blood cell (RBC) apheresis procedure. The plasma removed from the apheresis product and replaced in part with the PAS is not considered a concurrent component since you’re collecting only one product, and that is your apheresis platelet product. Then you’re further modifying that product by reducing the amount of plasma and replacing it with the PAS. The plasma removed from the platelet product is not specifically or separately collected. Therefore, it is not a co-component of the donation. Depending on how the plasma is processed, you can then label it as FFP, Plasma Frozen within 24 hours (PF24), or Plasma Frozen within 24 hours, held at Room Temperature for 24 hours (PF24/RT24).”

May 2019 *Babesia* Guidance

Background: Page 7, Section V.A.2 of the [May 2019 *Babesia* Guidance](#) states, “To comply with the requirements in [21 CFR 610.40\(a\)\(3\)](#), you must test donations as described in Section V.A.3. of this document or implement pathogen reduction technology (PRT) for platelets and plasma using an FDA-approved pathogen reduction device effective against *Babesia*, according to the manufacturer’s instructions for use.”

Questions:

- 4) What is the criteria for determining that a pathogen reduction device is “effective against *Babesia*”?
- 5) Who is responsible for making the determination that a device is “effective”?



May 2019 *Babesia* Guidance (cont'd)

FDA Response to Question 4: “The *Babesia* guidance was the first time FDA allowed selective testing, in 14 states, or use of pathogen reduction. FDA reviews submissions for pre-market approval of pathogen reduction devices. There is currently one approved device for platelets and plasma for transfusion. FDA’s review of the application and the data submitted determined that the labeled claim for the log reduction of *Babesia* is scientifically supported. The guidance allows its use instead of testing.”

May 2019 *Babesia* Guidance (cont'd)

ARS Response to Question 5:

Who is responsible for making the determination that a device is effective?



May 2019 *Babesia* Guidance (cont'd)

FDA Response to Question 5: “As we’ve already answered, FDA is responsible. Just a comment, that as new pathogen reduction devices are approved FDA will determine whether it is effective against *Babesia* and can be used as described in the guidance document.”

May 2019 *Babesia* Guidance (cont'd)

Background: Again, referring to Page 7, Section V.A.2 of the [May 2019 *Babesia* Guidance](#), “...you must test donations as described in Section V.A.3. of this document or implement pathogen reduction technology for platelets and plasma using an FDA-approved pathogen reduction device...”

Utilizing the current FDA approved pathogen reduction device, the determination that a platelet collection meets the guard-band requirements cannot be made until post-collection when the final collection volume and yield of the product is available. In many cases, samples have been simultaneously routed for *Babesia* testing in the event the product does not qualify for pathogen reduction.



CDC

May 2019 *Babesia* Guidance (cont'd)

Questions:

- 6) When a collection tests reactive for *Babesia* AND is also pathogen reduced, can it be distributed based on the use of PRT?
- 7) If not, does this apply to all collections that test reactive for a relevant transfusion-transmitted infection (RTTI), such as Zika virus (ZIKV)?
- 8) If so, and the product can be distributed, would FDA require the reactive test result to be placed on the label as described in [§606.121\(c\)\(12\)](#)?

May 2019 *Babesia* Guidance (cont'd)

ARS Response to Question 6:

When a collection tests reactive for Babesia AND is also pathogen reduced, can it be distributed based on the use of PRT?

Yes



No



May 2019 *Babesia* Guidance (cont'd)

FDA Response to Questions 6, 7, and 8: “The answer is no. The guidance recognizes *Babesia* as an RTTI and a transfusion-transmitted disease. An individual with evidence of an RTTI is not eligible to donate under [21 CFR 630.10\(e\)](#). Blood components from an individual who is infected with an RTTI are not suitable for transfusion. As described in the guidance in Section V.B.2, you must not ship or use a donation that is reactive for *Babesia* unless an exception for shipment or use is applicable as described in the *Code of Federal Regulations* (CFR) under [21 CFR 610.40\(h\)](#) and [21 CFR 630.30\(b\)](#). To summarize, the allowable exceptions are blood components for autologous use or documented exceptional medical need. The use of PRT is not an allowable exception that would allow distribution of a *Babesia*-infected unit.

This was a consistent theme, and the question was also about ZIKV. So, does this apply when there's a reactive test for an RTTI, does it also apply to ZIKV? The answer is yes. As stated in the ZIKV guidance, if a donation tests Individual Donor nucleic acid test (ID NAT) reactive for ZIKV, you must not distribute or use the donation unless an exception exists. Additionally, the use of PRT, as we've already described, is not an exception that would allow for shipment or release for transfusion.”

May 2019 *Babesia* Guidance (cont'd)

Background: Section V.B.3.b of the [May 2019 *Babesia* Guidance](#) provides for product quarantine of identified in-date cellular components collected from a donor in the 12 months prior to the date of a reactive index donation, including retrieval of in-date cellular blood components from consignees. The guidance does not provide recommendations for labeling or disposition of the products held in quarantine from prior collections.

Question:

9) How should we disposition these quarantined products?

FDA Response to Question 9: “The retrieved units must be either discarded or may be relabeled for research. While the guidance doesn't state this, the CFR does. So, retrieved units should be destroyed or relabeled for research.”



Along those lines, in the September 2019 Platelet Guidance

Background: According to the final guidance, Section III.B.1.c, Pathogen Reduction, “Platelets that have been treated by FDA approved pathogen reduction devices according to the device instructions for use need no further measures to control the risk of bacterial contamination of platelets.” My blood establishment intends to split a triple platelet collection and treat it as three single units. In some cases, we will PR two of the single units and then bacterially test the third.

Question:

10) If the bacterial culture of an apheresis platelet unit from the donation becomes positive, what actions should be taken on the three platelet co-components?

Along those lines, in the September 2019 Platelet Guidance (cont'd)

FDA Response to Question 10: “If a bacterial culture is positive, no component from the same collection may be distributed, per [21 CFR 606.145\(b\)](#). If one of the components from the collection has been pathogen reduced and already distributed before the culture became positive, the co-signee should be notified, and the unit retrieved if not yet transfused.”

Requirements for Licensed and Registered Facilities

Background: FDA regulations at [§607](#) require establishments that engage in the manufacture of blood products to register and list their products with the agency using the [Electronic Blood Establishment registration and Product Listing Form](#).

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



Requirements for Licensed and Registered Facilities (cont'd)

Question:

11) Two facilities are connected in some way (for example, part of the same hospital system, affiliated with, or have a contract with each other). One facility will provide crossmatched RBCs to another facility.

- What are the licensure and registration requirements if the two facilities are in the same state?
- What are the licensure and registration requirements if the two facilities are in different states?

Requirements for Licensed and Registered Facilities (cont'd)

FDA Response to Question 11: “The *Form 2830* no longer exists and has been obsoleted. You'll go ahead and register on the FDA website and you can print a report showing what products and activities you have registered for, but the actual form itself will no longer be available. So, just to clarify, that is a change in the registration policy. I'm going to answer both bullet parts of the question together. I'm going to assume that the facility that is providing the crossmatched blood is also performing the crossmatch. In this situation, that facility is performing activities that are consistent with the definition of manufacturer in [21 CFR 607.3\(d\)](#), specifically crossmatching and distribution. According to [21 CFR 607.20\(a\)](#), this facility must register and they should register as a hospital blood bank when they select the type of establishment.

Now if the hospital blood bank distributes the crossmatched blood to a facility that's within the same state, then only registration is required. However, if the hospital blood bank distributes the crossmatched blood to a facility in a different state, it's considered interstate commerce. As you heard at the CBER session yesterday, when a product goes into interstate commerce under the *Public Health Services (PHS) Act*, it must be licensed. To summarize, the location of the facilities, and not the business arrangements that exist, determines whether a product is in interstate commerce and needs to be licensed.”

Licensed Products, Regulated Products and Nonregulated Products

Background: Under [§601.2](#),

(d) Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products.

[42 USC 262 Regulation of biological products](#)

(a) Biologics license (1) No person shall introduce or deliver for introduction into interstate commerce any biological product unless-(A) a biologics license under this subsection or subsection (k) is in effect for the biological product;

The [October 2017 Circular of Information](#), Page 1 describes, “The blood components in this *Circular* marked with an ‘Ω’ are blood components for which FDA currently has not received data to demonstrate that they meet prescribed requirements of safety, purity, and potency, and therefore are not licensed for distribution in interstate commerce.”

Licensed Products, Regulated Products and Nonregulated Products (cont'd)

Questions:

12) Do facilities manufacturing unlicensed products, which would otherwise be considered “licensed products” in interstate commerce, also need to meet the safety, purity, and potency requirements of “licensed products” of the FDA?

13) If they do need to meet these requirements for safety etc., why do the reporting requirements under [§601.12](#) differ for licensed and unlicensed products, such as reporting changes associated with the [May 2019 Babesia Guidance](#)?

14) Sometimes products such as Thawed Plasma are discussed as products FDA does not regulate. Does this mean this is a product over which FDA has no regulatory authority?

Licensed Products, Regulated Products and Nonregulated Products (cont'd)

FDA Response to Questions 12 and 13: “The first question has to do with if a facility is manufacturing unlicensed products. Do we essentially expect for them to meet the safety purity potency requirements? The answer to this is yes, but let me tell you why. As you heard again in yesterday's CBER session, blood components are very special in that they also meet the definition of a drug. This means that they must follow both the blood good manufacturing practice (GMP) regulations in [21 CFR 606](#) and the drug GMP regulations in [21 CFR 210](#) and [21 CFR 211](#). The federal register preambles and the federal register preamble for the blood GMPs says the GMP regulations are intended to assure the production of blood and blood components of uniform high quality throughout the nation.

The same preamble says that the blood GMP regulations apply to all blood banks, transfusion services, plasmapheresis centers, compatibility testing, and all other facilities that process blood and blood components regardless of whether the products are intended for interstate or intrastate commerce use. To summarize all of this, the blood components must follow both the blood and drug GMPs for the manufacturing. The reason that that's in place is to ensure the availability of high-quality drug products, which includes blood, and to assure that all blood and blood components are safe, pure, potent, and effective regardless of where their distributor is or whether or not they're licensed.

Licensed Products, Regulated Products and Nonregulated Products (cont'd)

FDA Response to Questions 12 and 13 (cont'd): For the second question, it's important for me to give a little background. This has to do with why only licensed facilities report under [21 CFR 601.12](#) and unlicensed facilities do not. It's very important to distinguish between licensed and unlicensed facilities and licensed and unlicensed products. A facility that's identified as a licensed facility makes licensed products that are distributed in interstate commerce, and many of the licensed facilities also make unlicensed products that are only distributed within the state. A facility that's identified as an unlicensed facility only makes unlicensed products that are distributed within the same state. In order for a blood component to be licensed, the manufacturer of that component needs to submit a biologics license application (BLA). The BLA can only be approved after the manufacturer of the product has demonstrated that both the product and the manufacturing facility meet standards to ensure continued safety, purity, and potency of the products. Upon approval of the BLA, the manufacturer may place the U.S. license number on the product, and that approved product can then go into interstate commerce.

Now with that as background, let's go to the question. A manufacturer of a licensed product may determine that it's necessary to make a change to the way the product was manufactured. Under [21 CFR 601.12](#), manufacturers making licensed products are required to report changes to their BLA to FDA. Manufacturers making unlicensed products are not required to report changes in manufacturing. The reason for this is that unlicensed products are not part of an approved BLA. So, when changes are made to unlicensed products it doesn't impact the BLA.

Licensed Products, Regulated Products and Nonregulated Products (cont'd)

FDA Response to Questions 12 and 13 (cont'd): It is expected, as you heard in the previous response, that both licensed and unlicensed products must follow the GMP requirements in the CFR. I heard a phrase used in one of yesterday's sessions, 'there are no free lunches'. So, you might ask, 'If I make an unlicensed product and I don't have to report to FDA, how will FDA know if I'm following the GMP regulations?'. The answer to that is that all blood establishments, including licensed and unlicensed facilities or facilities making licensed and unlicensed products, are routinely inspected by our colleagues out in the field office. One of the things they do when they start the inspection, for all types of these facilities, is ask, 'What's changed since the last time we have been in your facility for the inspection?'. Then, the conduct of the inspection will include observing manufacturing, including manufacturer changes to processes, equipment, and products. So, no free lunch. Everything is overseen by FDA in some form or format."

Licensed Products, Regulated Products and Nonregulated Products (cont'd)

ARS Response to Question 14:

Sometimes products are discussed as products FDA does not regulate. Does this mean this is a product over which FDA has no regulatory authority?

Yes, FDA has no regulatory authority



26 Responses (19.26%)

No, FDA does have regulatory authority



109 Responses (80.74%)

Licensed Products, Regulated Products and Nonregulated Products (cont'd)

FDA Response to Question 14: “The correct answer is no. Blood and blood components or derivatives, including thawed plasma, are biologic products under the PHS Act, and biologic products, as we heard, also meet the definition of drugs under the *Federal Food, Drug, and Cosmetic Act* (FD&C Act). FDA currently has not received data to demonstrate that thawed plasma meets the requirements for safety, purity, and potency in order for thawed plasma to be licensed and entered into interstate commerce. We expect that blood establishments will follow GMPs for all of their products, including thawed plasma.”

Blood Supplied to Helicopters

Background: Our three hospital system is developing policies and procedures for supplying RBCs and plasma products on helicopters.

- The helicopter service is provided by a contracted vendor and the helicopters are parked at off-site base locations.
- Blood products are packed and transported via coolers specifically designed for “extended thermal performance” and have been validated for 24 hours.

At the helicopter base:

- The blood products may remain in the coolers for several days, with coolant materials changed every 24 hours.
- The cooler may be loaded on the helicopters and “transported” multiple times during this timeframe.
- If not transfused, the blood will remain in the cooler until returned to the Blood Bank.

All three hospitals **agree** that while the blood is in transport to each helicopter location, the blood must be maintained between 1 – 10 C. **They do not agree** on the status of the cooler (in transport or storage) and the appropriate temperature range once the blood is delivered to the helicopter base locations.

Blood Supplied to Helicopters (cont'd)

We want to remain in compliance and would appreciate information from the FDA.

Question:

15) What temperature range applies when a validated cooler contains blood for days at a time in an off-site location and are there any records required for receipt of the blood and the temperature?



Blood Supplied to Helicopters (cont'd)

FDA Response to Question 15: “Because RBCs and plasma are mentioned in the question, I'm going to cover both components. The question did not mention the thawing of the plasma outside the hospital setting. So, I'm going to assume that the plasma product that's supplied to the helicopter base is one that's already been thawed. [21 CFR 640.11\(a\)](#) and [21 CFR 610.53\(b\)](#) require RBCs to be maintained between 1 – 6 C during storage. [21 CFR 600.15\(a\)](#) requires RBCs to be maintained between 1 – 10 C during shipment. [21 CFR 640.34\(a\) and \(b\)](#) require frozen plasma to be stored at -18 C or colder. The *Circular of Information* states that thawed plasma should be stored at 1 – 6 C. [21 CFR 600.15\(a\)](#) also requires frozen plasma to be shipped at -18 C or colder.

This regulation doesn't address plasma that's already thawed, but I looked it up in the *AABB Blood Bank and Transfusion Service Standards* and they state that thawed plasma should be shipped at 1 – 10 C. Red cells and liquid plasma, or thawed plasma, are required to be stored between 1 – 6 C, and this is regardless of where they're stored and which device is used to store the products. These products are normally stored in a blood refrigerator that's validated to maintain the temperature between 1 – 6 C.

Blood Supplied to Helicopters (cont'd)

FDA Response to Question 15 (cont'd): We are aware that there are certain situations where storage containers or coolers are used for temporary storage. In these situations, the storage containers, even though they're just used for temporary storage, should be qualified for their intended use. The intended use is to maintain the products at the required 1 – 6 C during storage. The qualification of the storage containers regardless of what type they are, should include ensuring that they will maintain the required temperature, or the proper temperature for the time frame that is specified in your procedures.

To answer the specific question, as described, it sounds like the coolers are being used for storage and not transport. Therefore, according to the regulations in the applicable standards, the products must be maintained at 1 – 6 C. There is a second part to the question, 'Are there records required for receipt of blood and the temperature?'. The answer to that is yes. [21 CFR 606.160\(b\)\(3\)\(iii\)](#) requires records be maintained of storage temperatures. In addition, [21 CFR 606.165](#) requires records maintained for the distribution and receipt of blood components. Specifically, this regulation states that the distribution and receipt procedures must include a system by which the distribution and receipt of each unit can be readily determined to facilitate its recall if that becomes necessary.”

Donor Eligibility for Nonbinary and Gender-Neutral Donors

Background: Discussion continues surrounding appropriate methods to accommodate nonbinary and gender-neutral donors. Recently, a blood center received the following inquiry: “I am interested in donating blood, platelets, or other blood products. My gender is nonbinary, which is my legal gender on my driver’s license (‘X’). Will it be possible for me to donate with your organization and complete any required forms? Being required to select ‘male’ or ‘female’ is not something I am interested in doing.”

Questions:

16) What does FDA consider an acceptable approach to establish donor eligibility for nonbinary individuals who are otherwise eligible to donate?



17) Would answering all of the gendered questions on the Donor History Questionnaire (DHQ) be adequate to assess risk for transfusion-related acute lung injury, human immunodeficiency virus (HIV) and other infectious diseases, current pregnancy, and other donor safety concerns?

Donor Eligibility for Nonbinary and Gender-Neutral Donors (cont'd)

FDA Response to Question 16: “FDA’s [guidance document](#) on HIV risk, that was released in December 2015, recommends that male or female gender be self-identified and self-reported. We acknowledge that this recommendation did not foresee the issues that blood centers are encountering when perspective donors identify as both, fluid, other, or prefer not to identify as either male or female, or nonbinary. We recognize the complexity of gender identification and the challenges it poses to Blood Establishment Computer Systems (BECS) that require registration currently as either male or female. The responsible physician should explain to the donor the issues related to donor health and blood safety that currently depend on specifying male or female and the reasons donors are asked to self-identify for the purpose of blood donation.”

Donor Eligibility for Nonbinary and Gender-Neutral Donors (cont'd)

FDA Response to Question 17: “Yes. We are aware that some firms have taken the most restrictive approach to ask all donors all DHQ questions. This includes the pregnancy question, use of the most stringent deferral criteria for men who have sex with men or the 12-month deferral, the minimum hemoglobin of 13 grams per deciliter, and the use of appropriate apheresis device settings for collection. The firm should define their approach in their standard operating procedures and train staff accordingly.”

Donor Eligibility

Background: In the [December 2015 HIV Guidance](#) the donor deferral period for a nonsterile percutaneous inoculation, such as an accidental needle stick, is 12 months. A person who has injected an intravenous (IV) drug not prescribed by their physician, such as the one time use of an anabolic steroid 20 years ago, is permanently deferred. We understand the need for a permanent deferral for commercial sex work and IV drug abuse (without a prescription from their doctor), as these behaviors continue to place these individuals at a high risk for HIV.

[§630.10\(e\)\(1\)](#) describes:

Factors that make the donor ineligible to donate because of an increased risk for, or evidence of, a relevant transfusion-transmitted infection. A donor is ineligible to donate when information provided by the donor or other reliable evidence indicates possible exposure to a relevant transfusion-transmitted infection if that risk of exposure is still applicable at the time of donation.

Donor Eligibility (cont'd)

Question:

18) It is reasonable to conclude that any risk associated with a single payment of money for sex or use of a steroid 20 years ago would have resulted in a detectable infection and is no longer a risk. What is the basis for a permanent deferral for a single instance of prostitution or the one time use of an anabolic steroid 20 years in the past?

Donor Eligibility (cont'd)

FDA Response to Question 18: “As the introduction of this question states, the current recommendations are found in the [December 2015 HIV Guidance](#), and FDA stated the data at the time for commercial sex work and injection drug use are behaviors that continue to place individuals at a relatively high risk of HIV infection and a relatively high risk of window period transmission of HIV. The guidance stated, there is little data available on the HIV risk in individuals who have discontinued commercial sexual work and IV drug use regardless if it was ‘just once’ or remote in the past. So, at the time of the guidance there was no data. I'm not going to answer this question because I'm not going to make policy from the podium, but I am going to state that we are open to considering information that might support the safety of alternative strategies for evaluating the risk of these individuals who are currently indefinitely deferred for commercial sex work and IV drug use.”

Donor Eligibility (cont'd)

Background: Based on FDA guidance recommendations a permanent deferral is applied to donors:

- With a confirmed positive hepatitis B surface antigen - [Recommendations for the Management of Donor and Units that are Initially Reactive for Hepatitis B Surface Antigen \(HBsAg\)](#) 12/2/87
- Who has ever taken the drug Tegison (etretinate) - [Deferral of Blood and Plasma Donors Based on Medications](#) 07/28/93
- Who has received a dura mater allograft or pituitary growth hormone of human origin.
- [Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products](#) January 2016

Donor Eligibility (cont'd)

Permanent deferrals are required for individuals who have ever:

- had a confirmed positive hepatitis B surface antigen,
- taken the drug Tegison (etretinate),
- received a dura mater graft,
- received pituitary growth hormone of human origin.

Indefinite deferrals are required for individuals who:

- test reactive for hepatitis C Virus and/or HIV,
- are IV drug abusers.

Question:

19) What are the criteria used by FDA to determine the need for “permanent deferral” versus an “indefinite deferral” and the basis for these differences?



Donor Eligibility (cont'd)

FDA Response to Question 19: “A permanent deferral is generally used in guidance to refer to a confirmed diagnosis of a transfusion transmissible infection that can cause a chronic infection, such as being infected with HIV, hepatitis C, or hepatitis B, or the possible exposure to a pathogen with a long asymptomatic incubation period, such as the iatrogenic risk of CJD risk exposure, that require a permanent deferral with no chance for re-entry. An indefinite deferral is generally used in guidance documents to refer to the possibility, that at some point in the future, there will be an approved requalification method for these donors who are indefinitely deferred, such as donors who have falsely reactive tests for HIV, hepatitis C, or hepatitis B. Generally, just as we've discussed for the indefinite deferral for a history of injection drug use, we are open to discussions as new data become available that might support science-based decisions for alternative approaches for the indefinite deferrals.”

Blood Product Deviation (BPD) Reporting

Background: The [October 2006 Biological Product Deviation Reporting for Blood and Plasma Establishments](#) guidance provides FDA's current thinking related to BPD reporting and requires that blood and plasma establishments report to FDA product deviations in manufacturing that may affect the safety, purity, or potency of a distributed product.

[§606.171 Reporting of product deviations by licensed manufacturers, unlicensed registered blood establishments, and transfusion services](#) states:

(a) Who must report under this section? You, a licensed manufacturer of blood and blood components, including Source Plasma; an unlicensed registered blood establishment; or a transfusion service who had control over the product when the deviation occurred, must report under this section. If you arrange for another person to perform a manufacturing, holding, or distribution step, while the product is in your control, that step is performed under your control. You must establish, maintain, and follow a procedure for receiving information from that person on all deviations, complaints, and adverse events concerning the affected product.

BPD Reporting (cont'd)

Our facility stores RBCs and plasma in multiple, remote critical care areas. The products are stored in refrigerators maintained by the blood bank, and not crossmatched or tagged for a specific patient. A mislabeled (or unsuitable for any reason) product was transferred to one of these refrigerators, but the error was caught and corrected before it was retrieved for emergency patient use.

Question:

20) Would this be considered a mislabeled product issued from the Blood Bank which requires BPD reporting?



OR



BPD Reporting (cont'd)

FDA Response to Question 20: “[21 CFR 606.3\(k\)](#) defines ‘distributed’ to mean the blood and blood components have left the control of the licensed manufacturer of blood and blood components, unlicensed registered blood establishment, or transfusion service. In this scenario the product is considered distributed when it has left the control of the blood bank and been transferred to the remote refrigerator. The blood bank would no longer have control over that product. A nurse could go in and take the unit out of the refrigerator without blood bank intervention. Therefore, that product is considered distributed. So, if it was mislabeled, the blood bank would need to submit a deviation report for that.

I wanted to mention two things that are changing with the BPD reporting procedures. One of the guidance documents that's going to be updated by 2019 is the BPD guidance because of the changes that we've made over the last couple of years. To incorporate the new requirements under [21 CFR 630](#) for donor eligibility, we're in the process of updating our guidance. That's going to be another one that you'll see before the end of the year being updated. With the electronic biological product deviation website application for submitting deviation reports, we're in the process of making some changes to the platform to log into the system. That may happen sometime after the first of the year, but emails will go out to user accounts in plenty of time to notify you of when the changes are going to occur.”

Donor Eligibility

Background: Marijuana (cannabis) state laws are changing rapidly across the U.S. Donor eligibility and cannabis use has become a hot topic. The media is requesting a quote from our donor center on whether we allow individuals who use cannabis to donate, and do we test for cannabis.

Question:

21) What is FDA's position on blood donor eligibility with respect to cannabis use?



Donor Eligibility

FDA Response to Question 21: “The bottom line is determining whether or not the donor is eligible. The responsible physician must assess the eligibility of each donor. This assessment must ensure determining whether or not the donor is in good health according to the requirements in [21 CFR 630.10](#). Also, determination must be made as to whether or not the donor is able to provide reliable responses to the medical history questions and is not under the influence of any alcohol or drugs as required in [21 CFR 630.10\(e\)\(2\)\(vi\)](#). FDA issued a warning in July 2018 about severe illnesses that have resulted from the use of contaminated synthetic cannabinoid products, and I'm going to provide the [web link for that FDA warning](#) so it can be included on the slides.”

AABB Note: the link has been added above.

Duties of the Inspector

Background: In April 2019 FDA issued the Final Rule, [Removal of Certain Time of Inspection and Duties of Inspector Regulations for Biological Products](#). The rule amended the general biologics regulations in [§600.21](#) related to time of inspection requirements and removed the list of duties of the inspector in §600.22.

Question:

22) Does the removal of the list of duties for the inspector mean that FDA can enter and remain in an establishment without identifying themselves at the time of their arrival?

Duties of the Inspector (cont'd)

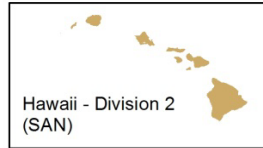
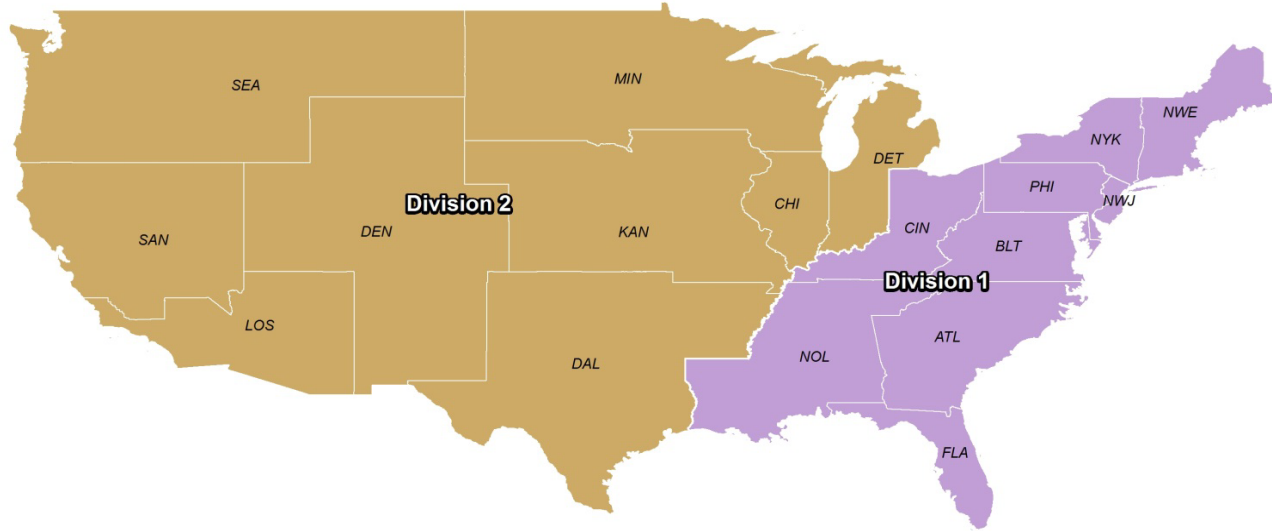
FDA Response to Question 22: “Per our procedures, upon arrival at your firm, every CSO, which we often refer to as an investigator, is required to introduce themselves and present their credentials to the top management official. After this, they will then issue a notice of inspection which we call our *FDA Form 482*. All inspections are not scheduled generally, and our inspections are not preannounced in advance, except for a few exceptions. Per Section 704 of the [FD&C Act](#), each inspection should be conducted at a reasonable time and within what is reasonably necessary to achieve the objective of the inspection.

To further clarify, the [Final Rule](#) does not change the biological product establishment inspection requirements and duties of an investigator that apply under Sections 704 and 510(h) of the FD&C Act and Section 351 of the PHS Act. In short, the Final Rule was updated to remove duplicative statutory requirements that were in both *21 CFR 600.22(a) through (h)* as well as in the Act. Another item of note from the Final Rule was regarding the frequency of inspection.

Duties of the Inspector (cont'd)

FDA Response to Question 22 (cont'd): Another item of note from the [Final Rule](#) was regarding the frequency of inspection. The removal of the biennial inspection for biological product establishments was replaced with the requirement that FDA inspect biological establishments in accordance with a risk-based schedule established by FDA. In turn, this means that the firm may or may not be scheduled to be inspected at intervals greater than or less than every two years. Some factors that are considered when scheduling inspections include the compliance history of your establishment, inherent risk of the products processed, and the nature of recalls linked to your establishment. Ultimately the resources saved by performing less frequent inspections at lower risk establishments will allow FDA to inspect those establishments deemed higher risk more frequently if needed.”

FDA/ORA Office of Biological Products Operations



Biologics Program Divisions

- Division 1 (ATL, BLT, CIN, FLA, NOL, NWE, NWJ, NYK, PHI, SZN)
- Division 2 (DAL, DEN, DET, KAN, CHI, LOS, MIN, SAN, SEA)
- FDA Current District Boundaries



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Susan Turcovski, Deputy Program Director

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Catherine Quinlan, Director Compliance Branch
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Who do I contact following my inspection?

ORA/Office of Biological Products Operations

Inspection-related correspondence e-mail box:

orabioinspectionalcorrespondence@fda.hhs.gov

Include:

- Firm Name
- City, State
- Date(s) of Inspection
- Unique FEI number

Files *larger than 100 megabytes* can be submitted as smaller files in separate emails or you can send an FTP link and password for file transfer.

FDA Contact Handout



U.S. Food and Drug Administration
Office of Regulatory Affairs
Office of Biological Products Operations (OBPO)
www.fda.gov

New FDA Contact Information

Your firm now has new FDA contacts to correspond with regarding your biologic products inspections.

Your inspections are now managed by the Office of Regulatory Affairs' Office of Biological Products Operations (OBPO).

Who do I contact following my FDA inspection?

E-mail your inspection-related correspondence to the email address listed below. Electronic responses are preferred, however, if hard copy responses sent via mail is the only way you can provide your response, please use the address of your firm's home district as listed on your FDA-482.

E-mail correspondence to orabioinspectionalcorrespondence@fda.hhs.gov

How do I submit my correspondence?

OBPO prefers e-mail correspondence. E-mail is preferred method due to a focus on efficiency, fiscal responsibility, and environmental awareness.

An acknowledgement of the receipt of your e-mail will be provided. You do not need to mail a back-up, physical copy. You can e-mail files under 100 megabytes to orabioinspectionalcorrespondence@fda.hhs.gov. Files larger than 100 megabytes can be submitted as smaller files in separate emails or you can send an FTP link and password for file transfer.

What other contact information do I need to know?

The Program Division Director (PDD) supervises all inspections and compliance activities.

- Elizabeth Waltrip (Division 1) - Elizabeth.Waltrip@fda.hhs.gov
- Kariton Watson (Division 2) - Kariton.Watson@fda.hhs.gov

The Director of Investigations Branch (DIB) and Staff Director manages all inspectional activities.

- Lisa Harlan (Division 1) - Lisa.Harlan@fda.hhs.gov
- Tricia Samaniego Martinez (Division 2) - Tricia.Martinez@fda.hhs.gov
- Travis Chapman (Team Biologics Staff, Division 1) - Travis.Chapman@fda.hhs.gov
- Colleen Hoyt (Team Biologics Staff, Division 2) - Colleen.Hoyt@fda.hhs.gov

The Director of Compliance Branch (DCB) manages FDA-483 responses and post-inspection compliance activities.

- Julie Bringger (Division 1) - Julie.Bringger@fda.hhs.gov
- Catherine Quinlan (Division 2) - Catherine.Quinlan@fda.hhs.gov

Why are you changing my FDA contacts?

In May 2017, as part of a broader agency initiative called program alignment, the U.S. Food and Drug Administration's (FDA) Office of Regulatory Affairs (ORA) implemented a program-based management structure that aligns staff by FDA-regulated product. This organizational approach replaces a management structure based on geographic regions. The changes within ORA are being made as part of the agency's Program Alignment strategy to modernize and strengthen the FDA's workforce and improve our public health response.

For more information on program alignment, visit:

<https://www.fda.gov/aboutfda/centersoffices/officeofglobalregulatoryoperationsandpolicy/ora/ucm549087.htm>

OBPO Reorganization FDA Commentary [slides 81-84]

Tricia Martinez:

“In addition to addressing the [Final Rule](#), I’d like to take a few minutes to give some insight on our recent reorganization as well as how to best contact our office, specifically as it relates to post-inspection correspondence. In May 2017, FDA’s ORA underwent their largest reorganization to date which is referred to as ‘Program Alignment’.

As you can see on the map, OBPO is split into two divisions. Division One, primarily covers our eastern half of the U.S. to include Puerto Rico. Division Two, where I sit, covers the western half to include Alaska, Hawaii and the Pacific Islands. As part of our reorganization, our new program-based management structure aligns staff by commodity. This approach replaces the previous management structure that many of you may be familiar with, that was based on geographic regions. The specialization by FDA product type more closely mirrors the organizational models of FDA Centers as well as the industries that we regulate. The goal of Program Alignment is to advance the effectiveness of our communications, our processes, our ability to keep pace with scientific innovation, and ultimately protect public health. The entire reporting chain for FDA's ORA inspection compliance, from the employees on the front lines, which you all often interact with as the field investigators, to the assistant commissioners at headquarters, are specialized in a particular commodity.

OBPO Reorganization FDA Commentary [slides 81-84] (cont'd)

Here is our management structure for the OBPO. Our management and staff are located throughout the country, including a handful that are with me here at this meeting today. Our organization is led by Dr. Ginette Michaud and Susan Turcovski. Each division is led by a Program Division Director, a Director Investigations Branch, a Staff Director, as well as a Director of Compliance. One question we often receive is 'Who do I contact after my inspection?'

OBPO prefers correspondence via email in order to focus on efficiency, be fiscally responsible, and promote environmental awareness. On the screen, you will see the email address of where all email can be sent. When submitting any correspondence, it's always best to include the following: your establishment name, the city and state, the dates of your inspections, as well as a unique FDA Establishment Identification number which is often the same as your registration number. I want to assure you that all correspondence sent to this email address is assessed on a daily basis and then forwarded to the appropriate person for follow-up. An acknowledgement of the receipt of your email will also be sent. Should you want to submit correspondence via hard copy, those documents would need to be submitted to the address on your firm's FDA *Form 482* and addressed to the Program Division Director of where your facility sits.

OBPO Reorganization FDA Commentary [slides 81-84] (cont'd)

Lastly I wanted to highlight a document, our FDA contact information. This is a document that should be handed out at every inspection, most likely to the top management official. Should you not receive this document, please do not hesitate to request this from your investigator prior to close out. This contains all of our contact information, depending again on the division in which you are located, and addresses the hard copy as well as how to electronically submit.”

BPAC

Background: According to the [FDA website](#), “BPAC reviews and evaluates available data concerning the safety, effectiveness, and appropriate use of blood, products derived from blood and serum or biotechnology which are intended for use in the diagnosis, prevention, or treatment of human diseases, and, as required, any other product for which the FDA has regulatory responsibility, and advises the Commissioner of Food and Drugs of its findings.”

Questions:

23) How are topics chosen for BPAC review and evaluation?

24) What determines whether a vote will be taken?

25) How often does BPAC meet?

26) Is FDA obligated to follow the recommendations of the BPAC?

BPAC (cont'd)

FDA Response to Question 23: “In general, advisory committee meetings are held at the discretion of FDA. OBRR, in consultation with CBER and other components of the agency, identifies topics on which BPAC will make recommendations to FDA. In doing so, we consider when it would be in the public interest to obtain advice from BPAC and for intended persons to present information and views at oral public hearing before the committee. However, certain matters are subject to a hearing before an advisory committee under the [FD&C Act](#), including the classification of medical devices. Under its charter, BPAC may function as a medical device panel under the FD&C Act and provide recommendations on device classification and premarket approval. For example, BPAC recently discussed the classification of Human Leukocyte Antigen, Human Neutrophil Antigen, and Human Platelet Antigen devices used in transfusion or transplantation.”

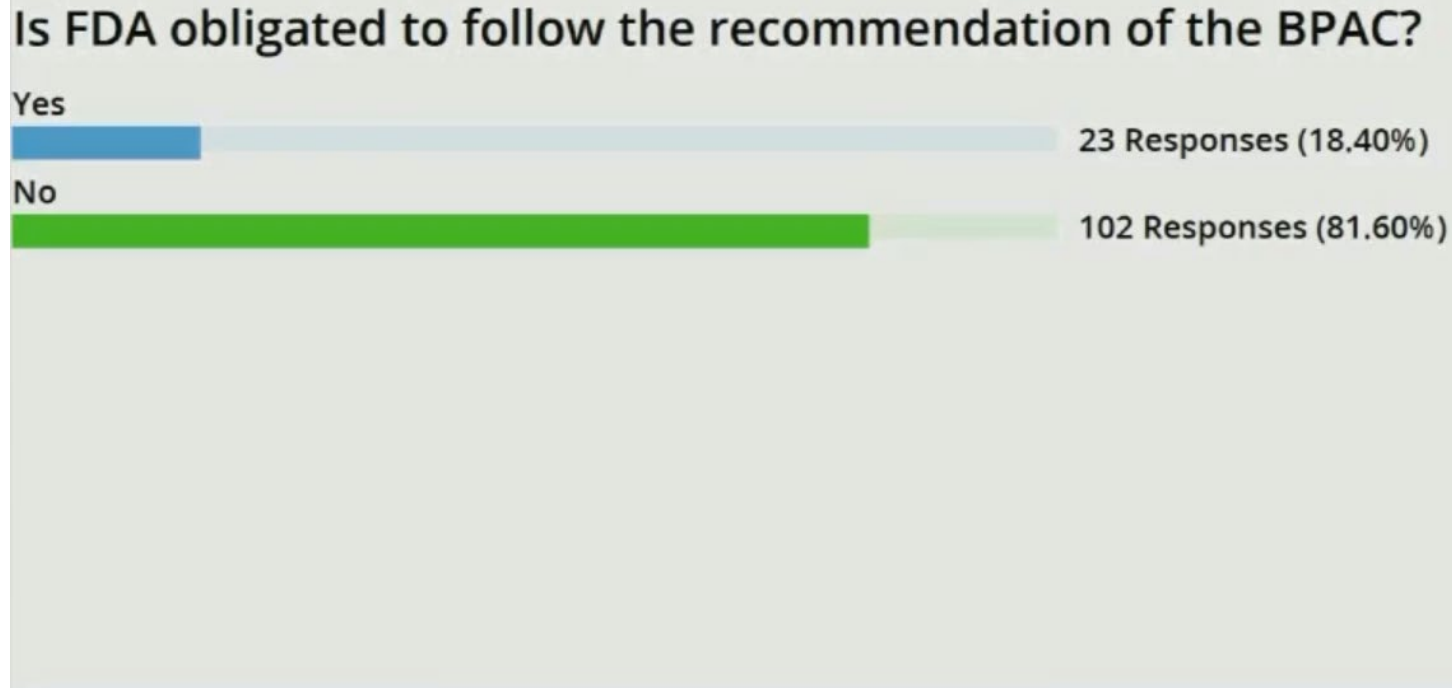
BPAC (cont'd)

FDA Response to Question 24: “Based on the advice we are seeking, FDA develops the questions that will be discussed by the committee. FDA will request committee members to vote on particular questions or in some cases provide comments and general recommendations to FDA on a particular topic.”

FDA Response to Question 25: “BPAC typically meets approximately two to three times per year and according to [21 CFR 14.20](#), all advisory committee meetings must be publicly announced at least 15 days in advance of the meeting date. As we heard today, there's one on Nov. 22, 2019. The notice must also include a list of all agenda items and state whether the meeting topics will be open or closed to the public. Generally, CBER aims to announce tentative meeting dates for the coming year on its website, and the topics are later announced in the *Federal Register*.”

BPAC (cont'd)

ARS Response to Question 26:




BPAC (cont'd)

FDA Response to Question 26: “FDA's advisory committee meetings, including BPAC, provide independent expert advice to the agency on complex scientific, technical, and policy issues, and they are a valuable resource to make important contributions to the agency’s decision-making process. While we carefully consider the recommendations made by the advisory committees, we are not required to adopt those recommendations. So, the correct answer is no. Under [21 CFR 14.5](#), the commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee.”

ZIKV Testing Requirements

Background: Discussion at the [March 2019 BPAC](#) included an FDA [presentation](#) on alternative strategies to universal ZIKV testing based on a decline of ZIKV in the U.S. and the Americas. FDA commented that they are re-evaluating the [July 2018 recommendations](#) for universal testing of blood donations using Minipool or ID NAT, presenting three testing strategies. FDA did not propose pre-donation assessment for ZIKV risk factors such as exposure through travel or sexual contact. The options presented were:

Options 1-3: 

1. No policy change; continue universal testing for ZIKV by MP or ID NAT
2. Regional testing for ZIKV with MP or ID NAT; with considerations for regional options
3. Eliminate all testing for ZIKV

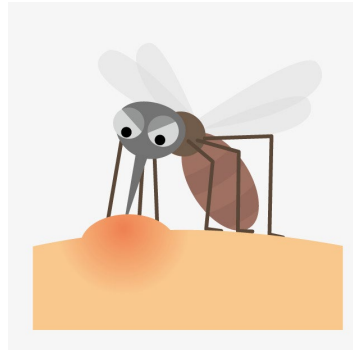
ZIKV Testing Requirements (cont'd)

Following discussion and voting, the Committee felt that additional information and continued surveillance and reporting is needed. Based on a continued decline in ZIKV reactive reporting, the topic should be reconsidered in a year or two.

Questions:

27) We have just completed another season of continued decline in ZIKV reactive reporting. Will FDA revisit the topic next spring or fall?

28) Would FDA consider a selective testing strategy for West Nile Virus (WNV)?



ZIKV Testing Requirements (cont'd)

FDA Response to Question 27: “To answer the first question, yes. At the March 2019 BPAC, the Committee voted in favor of continuing universal testing by minipool or ID NAT, as recommended in the final guidance, but the general discussion was that the issue should be re-evaluated after another year.”

FDA Response to Question 28: “We're open to further discussion about the safety of an alternative testing strategy for WNV, but we know that WNV is different from ZIKV. There are cases of WNV in the U.S. every year in almost every month. The question was considered previously, but we could revisit whether the data supports seasonal and/or regional testing for WNV. The CFR states that, in [21 CFR 610.40](#), if based on evidence related to the risk of transfusion, testing each donation is not necessary to adequately and appropriately reduce the risk of transmission, you may adopt an adequate and appropriate alternative procedure that is found acceptable for this purpose by FDA. If you're thinking about this question, such support for the determination that testing each donation for WNV is not necessary might be provided from epidemiologic evidence, for example, related to the seasonality or geographic distribution of WNV in the U.S.”

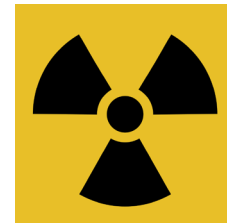
Cesium Irradiator Replacement Project

Background: The National Nuclear Security Administration (NNSA), Office of Radiological Security (ORS) is working with U.S. blood banks and donor centers who are interested in converting from cesium-137 blood irradiators to viable non-radioisotopic alternatives, such as X-ray irradiators. The Cesium Irradiator Replacement Project (also known as CIRP), offered by NNSA's ORS, provides [information](#) and financial incentive towards the purchase price of a new irradiator, as well as the removal and disposal of the cesium irradiator. ORS information compares the RadSure 3400, Best Theratronics MK1 and MK2 as alternatives to cesium irradiators.

Questions:

29) Are these three irradiators as effective as the cesium irradiators in preventing graft versus host disease (GVHD)?

30) What X-ray irradiators are FDA approved for this purpose?



Cesium Irradiator Replacement Project (cont'd)

FDA Response to Question 29: “Yes. While gamma rays and x-rays differ in how they are produced, they have the same radiation characteristics, and they inactivate lymphocytes in the same manner. Validation studies should be performed to establish the performance of the irradiator and maintenance procedures established to ensure a satisfactory ongoing performance.”

FDA Response to Question 30: “Blood irradiators, to prevent GVHD, are medical devices regulated by the Center for Devices and Radiological Health (CDRH). A number of x-ray-based blood irradiators have been cleared or approved by CDRH with an indication to prevent GVHD, including those noted in the question. Blood establishments should refer to a particular device ‘indications for use’ when considering an x-ray based blood irradiator.”

Use of Low-titer Group O Whole Blood in Emergency Situations - Reporting Category and Labeling Requirements

Questions:

- 31) Under [§601.12 Changes to an approved application](#), how do I report the manufacture of low-titer group O Whole Blood to FDA?

- 32) Where on the product label is it acceptable to include Anti-A and Anti-B titers?

Use of Low-titer Group O Whole Blood in Emergency Situations - Reporting Category and Labeling Requirements (cont'd)

FDA Response to Question 31: “Since this change has a minimum potential to have an adverse effect on the identity, strength, quality, purity, and potency of the product, as it may relate to the safety and effectiveness of the product, licensed firms may report the manufacturer of this product in an annual report, as stated in [21 CFR 601.12\(d\)](#).”

FDA Response to Question 32: “As far as including the Anti-A and Anti-B titers, if you're using the International Society of Blood Transfusion (ISBT) format for labeling your blood components then you should follow the format described in the *United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128*. The latest version available is [Version 3](#) dated March 2013.”

Ask the FDA

Cellular Therapy

Is this Legit?

Background: In March of this year, FDA issued a [Statement of Caution for Infusion of Young Donors Plasma](#), warning consumers of treatments which had not been evaluated or approved by FDA and which had no “clinical benefit for the uses for which these clinics are advertising them and are potentially harmful.”

Everyday we see new purported uses for platelet-rich plasma (PRP). For example, hair restoration claiming, “increasing evidence supporting its efficacy as an off-label treatment for hair loss.” and that “Most patients will need to go through multiple rounds of PRP over the course of several months...”



Is this Legit? (cont'd)

Question:

33) When we see, or are made aware of questionable claims involving the use of PRP, stem cells or other biologics should this be reported to FDA, and if so by what mechanism?



Is this Legit? (cont'd)

FDA Response to Question 33: “The answer is that FDA is concerned about questionable claims, and we do encourage the public to report them to us. There are several mechanisms, but the easiest way is to contact the Office of Communications Outreach and Development (OCOD). This information is available at the FDA website. OCOD has an email address at OCOD@fda.hhs.gov. There's also a 1-800 number, 1-800-835-4709, and a local number, 240-402-8010. I also want to put in a plug for the FDA CBER booth in the exhibit hall. I believe this is your last chance. It is being manned by OCOD, so you can just stop by and say hello.”

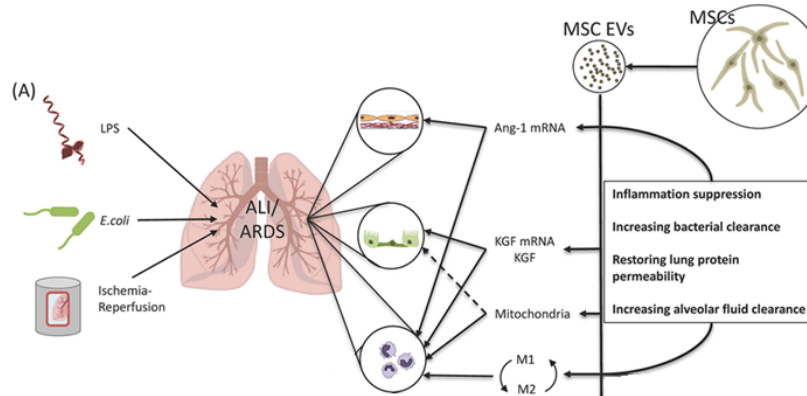
Regulation of Extracellular Vesicles

Background: New technology applications include cell-based products such as exosomes and those derived as byproducts from expanded cells, for example extracellular vesicles from mesenchymal stromal cells as potential therapies.

FDA regulation of HCT/Ps 361 vs 351

Question:

34) Will exosomes and cell and tissue based products, when they are the secreted material of a cellular product, be regulated under Section 351 of the PHS Act?



Adapted from *Transfusion*, Jae Hoon Lee et al. 2018

Regulation of Extracellular Vesicles (cont'd)

FDA Response to Question 34: “Thank you for this question, but there's really not enough information here provided to answer it. We don't really know what the product is. We don't know what the indications are. The regulatory pathway for the product depends on multiple factors, but we do want to say that if you are unsure about how a product will be regulated, you have several options. There is information on the FDA website, or if you visit the booth there's also information in a handout. The three options are you can contact the OCOD, you can send an email to the TRG or Tissue Reference Group Rapid Inquiry Program, and that's a new program that is designed to have a two or three or four day turn around to have a response, or you can also submit a Request For Designation or RFD to the Office of Combination Products. Again, all of this information is available on the FDA website.”

ZIKV (Travel Information)

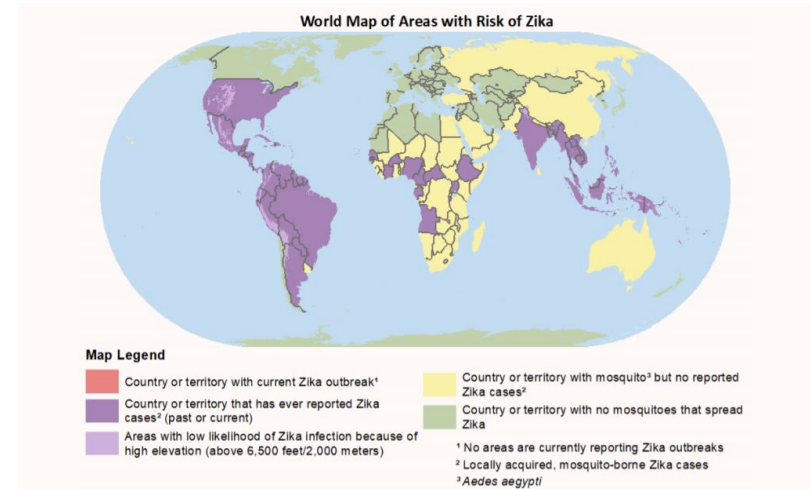
Background: When one looks at the FDA guidance areas of increased risk for ZIKV transmission it refers to CDC website's Zika map. The Zika travel page shows no current outbreak in the US as of the last update (Feb. 28, 2019). There are no current ZIKV outbreaks shown in red. The travel deferral is particularly affecting public cord blood donors.

Questions:

35) Are all purple areas excluding the U.S. considered a travel risk for donation?

36) What about U.S. territories like Puerto Rico?

37) What is the process for updating the map, and is there a way to have more real time data?



ZIKV (Travel Information) (cont'd)

FDA Response to Question 35: “For the purposes of screening donors of HCT/Ps, establishments should continue to use FDA CBER’s guidance for industry titled [*Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells Tissues and Cellular and Tissue Based Products*](#) that was updated in May 2018. Residence in or travel to an area with increased risk of ZIKV transmission in, or sex with a person known to reside in or travel to an area with increased risk of ZIKV transmission, are considered ZIKV risk factors for the purposes of determining eligibility of living donors of HCT/Ps. FDA considers countries and territories outside the U.S. states, categorized as red or purple, as areas of increased risk of ZIKV transmission. Therefore, a donor of HCT/Ps who resides in a country colored purple or red should be determined ineligible.”

ZIKV (Travel Information) (cont'd)

FDA Response to Question 36: “Puerto Rico is outside the U.S. states and it is colored purple. Therefore, donors who reside in Puerto Rico or who have traveled there within the past six months are ineligible. Donors of umbilical cord blood, placenta, or other gestational tissues who have resided in Puerto Rico or have traveled to Puerto Rico at any point during the pregnancy are ineligible.”

FDA Response to Question 37: “The world map on the [Blood and Tissue Safety Page](#) on the CDC website is maintained by the CDC. The CDC controls the content of this webpage, but if you have comments you can also provide them to the CDC.”

ASK CMS/CLIA

CLIA Certificate Requirements

Background: Per AABB Cellular Therapy Reference Standard 5.17B Part 4:

4. Tests for microbial contamination (culture for aerobic and anaerobic bacterial and fungal elements) shall be performed on a sample obtained after processing but before the addition of cryoprotectant solution if the cryoprotectant is cultured separately or purchased as sterile and connected as closed system. Otherwise, microbial testing shall be performed after the addition of the cryo-protectant. If results affect the donor's health or the therapeutic value of the product, notify the donor's physician or donor's mother and recipient's physician of positive culture results.

Question:

38) If my facility performs this testing is it required that we have a CLIA certificate to do so?

CLIA Certificate Requirements (cont'd)

CMS Response to Question 38: “Before I answer the question, I'd like to say that the answers that I'll be giving to the questions today are based on CLIA regulations. However, I would like to remind you that many laboratories choose to obtain their CLIA certification through a CMS approved accreditation organization, of which there are seven, one of which is AABB. These laboratories must follow all the requirements of their chosen accreditation organization, which may be more stringent than our CLIA requirements. With that being said, I will answer the question. CLIA applicability is key to the definition of a laboratory in the CLIA regulations at [42 CFR 493.2](#).

So, the answer to the question is yes, a CLIA certificate of compliance or certificate of accreditation is required because the results of microbial contamination testing may be communicated following the facility's notification policies and used for the assessment of health or diagnosis of disease. Sterility testing is subject to CLIA regulations as described in CMS survey and certification letter 11-08-CLIA titled *CLIA Applicability for Laboratory Testing Associated with Cells, Tissues, Blood and Organs*. This [survey and certification letter](#) can be found on the CMS website.”

CMS Surveyors

Background: I am interested in knowing the CMS National Office's interpretation of [42 CFR 493.959](#) which lists compatibility testing as a test regulated under CLIA.

Question:

39) Does the electronic crossmatch fall under the category of compatibility testing and if so, where can we find a CMS-approved proficiency testing program for the electronic crossmatch?

CMS Surveyors (cont'd)

CMS Response to Question 39: “The electronic crossmatch is a process of ensuring that blood released for transfusion is compatible with a specified recipient by means of electronically matching patient pretransfusion test results, such as ABO, Rh, antibody screen, etcetera, with the information about the blood donor that is stored in the BECS. For the electronic crossmatch, the CLIA regulations require compatibility testing following FDA requirements at [21 CFR 606.151\(c\)](#). There is no CMS approved proficiency testing program for the electronic crossmatch. Thank you.”

CMS Surveyors (cont'd)

Background: [§493.1451\(b\)\(8\)](#) lists the six methods that must be used for competency assessment. We are a hospital system comprised of eight hospitals. All eight transfusion services operate under the same policies, processes, and procedures, and employ the same methods for blood bank testing. Our technologists can be scheduled to work at any of the eight transfusion services.

Question:

40) Must competency assessment be documented at each of the eight sites at which they work, or will one competency assessment that includes all six methods suffice?



CMS Surveyors (cont'd)

CMS Response to Question 40: “Generally, there is one CLIA certificate for each laboratory location, and each laboratory is responsible for complying with the applicable CLIA requirements. In the situation described in this question, each of the eight hospitals would have a separate CLIA certificate. Therefore, each hospital is responsible for performing and documenting its own competency assessment. The interpretive guidelines for [42 CFR 493.1451\(b\)\(8\)](#) state that all testing personnel must be listed on the CMS 209 laboratory personnel report and must undergo documented competency assessment, using the six procedures denoted under the technical consultant or technical supervisor’s responsibilities for all testing performed.”



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