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FDA Review of Biologics License Applications for Blood and Source Plasma
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>> ANNE EDER: Good morning. And welcome to our webinar. I'm Anne Eder, the Director OBRR, the Office of Blood Research and Review. I'm glad you're here.

We're on FDA's beautiful White Oak campus. This is a picture. It's particularly beautiful in the spring, when everything blooms and wildlife emerges again. We have over 700 registrants today across the U.S. and internationally.

So it's wonderful to see such broad interest. And I welcome everybody. But I want to say at the outset that the workshop will address blood establishments, U.S. blood establishments that collect blood and blood components for further transfusion. And so as plasma for further manufacturing of plasma, plasma therapeutics.

And I mentioned the campus, it truly is a beautiful, sprawling campus. And we designed this webinar to address, to try to address should go for everyone whether you're a new licensed applicant, just opening a center, just getting started in the world like this gosling that parades around our campus in the spring or whether you're a mature established firm and you're acquiring a new facility or submitting a a supplement, making a change to your approved application.

I also want to say that this webinar will not address gene therapy or cell therapy. OBRR, the Office of Blood does not regulate those products. Our sister office, the Office of Therapeutic Products regulates those products. But you're in luck because the Office of Therapeutic Products is holding a townhall for best practices for preparing BLA submissions for cell and gene therapy products on June 4.

We also will not be addressing tissues or tissue-based products, umbilical cord blood, platelet rich plasma or devices that manufacture, that produce platelet rich plasma at the point-of-care or devices or *in vitro* diagnostics, even though the Office of Blood regulates devices and *in vitro* diagnostics. That will not be covered in today's, the regulation of those devices will not be covered in today's workshop.

Blood and blood components in the U.S. are essential to healthcare. From the National Blood Utilization and Collection Surveys published in 2025, we know that in 2023, from the survey published in 2025, over, or around 12 million units were collected. And over 13 million donations were screened or tested from about 6.5 million unique donors.

For Source Plasma, we don't have a publication like the National Blood Collection and Utilization Survey. but we know that over 50 million liters of Source Plasma are collected. And U.S. Source Plasma collectors provide or collect and provide over 70% of the global supply of Source Plasma for plasma therapeutics.

This slide shows the number of registered and licensed and registered-only blood establishments in the U.S. And the number of licensed Source Plasma centers. This slide shows numbers, of course. But it actually tells an important story of the U.S. blood supply. And that is, that licensed blood centers can distribute blood across state lines. Whereas registered-only blood centers can't. They can only distribute blood within the state in which they collect blood. They can distribute blood within the state, even when we're reviewing their applications. What's important to understand is that, when blood is needed during an emergency, in every mass casualty event, actually I also want to point out just to make the point that licensed and registered blood establishments must meet the same regulations. So everything that we present today applies to both registered and licensed blood establishments.

But what's important to understand, uh, is that, when blood is needed in a mass casualty event, licensed blood establishments have worked together to get blood where it's needed in the U.S. so when blood is exhausted, when the blood supply is exhausted and in one part of the U.S., blood centers, licensed blood centers move blood to where it's needed. It's the blood on the shelf that saves lives, immediately.

So it's not opening new centers, it's not, you know, in the throws of the disaster, it's not quickly opening centers even quickly after the disaster, but blood centers have shown time and time again, in every disaster, it's moving blood to where it's needed.

What we learned in COVID conversely is that-- so I also wanted to point out, that there are 71 licensed holders. And of these, the four largest license holders provide about 50% of the blood in the U.S. So we have a lot of licensed holders, and a lot of those license holders, have a lot of blood centers. So we review a lot of supplements which you'll see in a future slide. So sort of the converse situation is in the lesson that we learned in COVID - if we learned an important lesson, one of the important lessons we learned from the pandemic, was that the smaller centers, the registered-only centers, could open, make changes more quickly, could get changes implemented more quickly than the larger centers. They were much more nimble it seemed, some of them. And - this is an oversimplification - but the point I'm trying to make is that some blood establishments are able to open new centers and make changes that meet all FDA requirements more quickly than others.

So, the goal of this workshop and what we hope you'll take away from it are, is the information that you need, so that you'll be one of the quick ones. You'll be one of the ones who can put

together a complete application that will result in a smooth and quick approval because our country needs a safe, available, and stable blood supply.

So the Office of Blood Research and Review regulates the blood supply essentially through these activities, primarily through regulatory review. And we regulate blood and blood components. That's why we're here. That's the focus of this webinar. We regulate Source Plasma, we also regulate devices for manufacturing. As I said, that's not the focus of this webinar, but we regulate the donor screening tests, the confirmatory screening tests, that we use for blood donation. We regulate the collection sets. Basically, everything that's used to collect blood and manufacture it and store it and provide it for transfusion. We regulate it. Immunohematology reagents, the blood establishment computer software. We perform inspections which you'll hear about today. We're involved in compliance when there needs to be investigations. We've developed policy which you'll also hear about today, and preparedness. And our branches also perform mission-related research.

This is our organization. I'm the Office Director. Dr. Oreiji Illoh is the Deputy Director, really the Co-Director of the Office. We have two divisions, the Division of Emerging and Transfusion Transmitted Disease and the Division of Blood Components and Devices. The divisions have product review branches that perform full-time products review and lab research branches that perform primarily the mission-related research. But the scientists in those branches also perform reviews, when needed.

We have in the Division of Blood Components and Devices, and you'll hear us refer to DBCD, many acronyms, but we'll try not to use acronyms so you'll know what we're talking about in our organization. But today, the focus and the spotlight is on our Blood and Plasma Branch or BPB. The Blood and Plasma Branch reviewed 461, and that's pretty much around 500 submissions a year, and this is how they break down. This is how, they, the categories they fell into in 2025. Original BLAs, mostly supplements or changes to approved applications which you'll hear about today. These are the number of pre-approval inspections performed in recent years across the country for Source Plasma establishments and blood establishments, you'll hear about today. And these are our dedicated staff in the Blood and Plasma Branch. This is our faculty who will be presenting today. And we put together, like I said, a very broad. We tried to design a curriculum today that has information for newcomers and experienced blood establishment. We think we've developed material for pretty much beginners and experienced blood establishments. So I hope you enjoy what we've put together for you. We really want you to succeed. So enjoy the day. And I'll come back in the end and make some closing comments and summarize resources that we're providing to you. So thank you, thank you for joining us. And I'm going to introduce Dr. Wendy Paul, the Director of DBCD who is going to moderate our session, introduce you to our speakers today. So thank you very much. And enjoy our program. Thank you.

>> WENDY PAUL: Good morning. I am Wendy Paul, the Director the Division of Blood Components and Devices. I'd like to thank Dr. Eder for sharing and engaging in high level view and introduction to the work performed in OBRR and its importance to ensuring sustainable and safe U.S. blood supply.

Today, we're going to zoom in and give you a ground level view of the work being performed by the Blood and Plasma Branch. And since they are the star of the show, I am going to refer to them as BPB.

But BPB is going to give you a workshop that will really be educational. I'm very excited to be a part of this OBRR workshop faculty who are all experts in their field and extremely committed group of scientific regulatory professionals.

Today's agenda as Dr. Eder mentioned is filled with informative presentations to provide the information you will need to submit a successful BLA application for FDA review. The objectives for this workshop are-- to describe the FDA regulatory requirements for the manufacture of blood and blood components, including Source Plasma.

Identify testing, donor deferral and notification requirements for relevant transfusion-transmitted infections and donor reentry recommendations. Explain the requirements and process for blood establishment the registration. Describe the steps in submitting a biologic license application for blood and blood components. Explain the BLA review process and common deficiencies in submissions and to describe the pre-license and pre-approval inspection process and common citations.

As I said, today's agenda is full. So to boil it down to its simplest terms. And if you're into cooking, you might understand the redux version of our objectives are, what you need to know about regulatory requirements, RTTI testing, donor deferral, notification, and reentry. We also want you to take away what you need to do to register, to submit a BLA license application, what you need to do during the BLA process to avoid common deficiencies and what you need to do during an inspection to avoid common citations.

After the presentations, there will be a question-and-answer period where our BPB reviewers will respond to questions that were submitted in advance of the workshop. And as Dr. Eder mentioned, she will come back for closing remarks.

So having said all of that, let's get started.

Our agenda will be divided into three parts. Part one, two, and three-- for part one, the faculty and their presentations are, Jennifer Scharpf, our Associate Director for policy in OBRR will be presenting regulatory requirements for blood and blood components including Source Plasma.

The second presentation will be by Dr. Yeowon Kim in Medical Officer within OBRR. And she'll be presenting donation testing, donor deferral, requalification and notification.

The third presentation for part one is presented by Carmelita Bibby, a consumer safety officer in BPB. She will be presenting blood establishment registration and facility relocations.

At the end of Carmelita's presentation, there will be a 15 minute break. And we'll resume with part two. Thank you and I look forward to seeing-- oh, I'm sorry. I'm going to go through the entire agenda.

Part two of the agenda, the faculty will be Miriam Montes, the branch chief for BPB. She will be presenting submitting a BLA for bloods and blood components or Source Plasma. The second speaker in part two is Camilla Smith, the team lead for BPB. She will be presenting biologics license application review process.

And the final speaker in part two is Catherine McGraw, a consumer safety officer within BPB. And she will be presenting the FDA OBRR inspection process, expectations, and common citations. There will be another 15 minute break, and when you return, we will have part three of the workshop.

This will consist of our Q&A session where Miriam Montes and Camilla Smith will respond to questions submitted in advance. And then you will have closing comments by Dr. Eder. We'd like to thank you for attending, and now I would like to present our first speaker, Jennifer Scharpf.

>> JENNIFER SCHARPF: Good morning. Welcome and thank you for participating in today's workshop. My name is Jennifer Scharpf. And I'm the Associate Director of policy for OBRR. And in this role, I direct OBRR's policy initiatives including the issuance of guidance documents and regulations, respond to legislative initiatives, and collaborate with colleagues across CBER and FDA on issues pertaining to the regulation of biologics and devices.

So the objective for this session is to discuss FDA's regulatory requirements for the manufacture of blood and blood components including Source Plasma.

And to accomplish this, I will first review FDA statutory authorities, provide historical perspective as well as review our current authorities; I'll review the code of federal regulation including regulations specific to blood and blood components. And then we'll discuss guidance documents and how OBRR develops documents.

So statute is a law enacted by the legislative branch of government. And for the purposes of today's presentation, I will focus on statutes enacted by the U.S. Congress that provide FDA its authority for the regulation of biological products including blood and blood components.

So dating back to the late 19th and very early 20th Century, the Federal Government recognized the need for enhanced regulation of biological products. Congress passed the Biologics Control Act of 1902. And defined biological products as any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention and cure of diseases of man. And it's highlighted in red on the slide the Biologics Control Act address the need for licensure of biological products and interstate commerce.

The statute recognized the need to focus on the manufacturing of biological products and contain language that quote, the purity of the substance which is refer to go a biologic is far more important than the purity of ordinary drugs.

The statute also authorized the hygienic laboratory which was established in 1887, and was a precursor agency to the National Institute of Health to issue regulations that govern all aspects of the commercial production of biological products and conduct inspections.

And although it's not on the slide, I'd like to mention that in 1930, be the hygienics laboratory became the National Institute of Health. And in 1934, NIH issued the first regulations requiring proof of potency for licensure of biological products.

So in 1944, the Biologics Control Act was reenacted as section 351 of the PHS Act. At the same time, section 361 which requires control of communicable diseases was enacted. And at the time, the definition of biological products in the PHS Act did not include blood and blood components. In 1947, regulations were issued under which blood and plasma were designed as analogous products under the statutory definition of biological product. And this was in response to concerns in the contamination of the blood supply during World War II. However these regulations were challenged. And in 1968, the fifth circuit court held that the regulation was beyond the scope of the Public Health Service Act.

So to ensure that the act was applicable to blood and blood components, in 1970, Congress amended the definition of biological product via legislation to add blood, blood component, and derivatives to the definition of biological product.

In 1972, the regulation of biological products moved from the NIH Division of Biologics Control to the FDA Bureau of Biologics.

And the PHS Act has been amended many times since 1944. But one of the most significant changes was the addition of section 351K in 2010 to design biosimilarity and provide abbreviated pathway for license sure for biosimilar products.

So the current definition of biological product in the PHS Act is provided in this slide. And most importantly for this audience, blood, blood component and derivatives are within the definition. And biological-- the definition of biological products is also provided in the regulations at 21 CFR 600.3H.

The two sections of the act most applicable to to FDA are sections 351 and 361. Section 351 requires license for distribution of any biological product in interstate commerce including blood and blood components. This section establishes that the biologics license application or BLA must demonstrate that, one, the product is safe, pure, and potent. And two, that the facility meets standards to ensure that the product continues to be safe, pure, and potent. And this establishes the requirement for facility inspections for biological products.

Section 361 provides the Federal Government authority to issue regulations to prevent communicable diseases which is paramount to the regulation of the blood supply. This section gives FDA the authority to regulate all blood and blood components and not just those in interstate commerce in order to prevent the transmission of transfusion transmitted infections.

Blood is also regulated as a drug under the Federal Food, Drug, and Cosmetic Act. Section 351j of the PHS Act clarifies that the FD&C act applies to biological products. Blood is a drug because blood components are intended for use in a diagnosis, cure, mitigation, treatment or prevention of diseases in men. And blood and blood components are generally subject to the FD&C Act including the requirements for good current manufacturing practice, prohibitions on adulteration and misbranding of products and inspection of manufacturing facilities.

So next I'll transition to discussing the regulations that implement the Public Health Service Act in the Food, Drug, and Cosmetic Act. Over the next few slides, I'll provide a high level overview of regulations. Regulations also called rules are requirements set by a government agency under the statutory authority from Congress. And as we just discussed, FDA's authority to conduct rulemaking is in the FD&C Act and the PHS Act. Regulations have the force and affect of law and provide more detailed legal standards and greater clarity than what is described in the underlying statute.

And regulations are also intended to help ensure the uniformity of enforcement of the underlying law.

So the Administrative Procedures Act which was enacted in 1947, establishes procedures that Federal Agencies must use for rulemaking and ensures public access to and participation in rulemaking. Under notice and comment rulemaking, agencies publish a proposed rule in the Federal Register. This helps to ensure public participation in the rulemaking-- through written comments. Once, after an agency considers all the public comments, the final rule is then issued. That includes the codified text and as well as a detailed preamble that responds to the public comments and provides the basis for the regulation.

The preamble also describes how an agency is complying with other statutes such as the Paperwork Reduction Act which addresses collections of information and the National Environmental Policy Act which addresses environmental assessments on certain federal actions.

All planned regulatory activities are included in the Unified Agenda which is published by the Office of Management and Budget or OMB. And the Unified Agenda provides a list of upcoming regulatory and deregulatory actions, activities by all Federal Agencies. It is intended to increase transparency and is used to signal an agency's regulatory priorities. The Unified Agenda is available at the link provided on this slide. And to locate FDA's priorities you would search under the Department of Health and Human Services.

FDA's regulations are in title 21 of the code of federal regulations or CFR and contained over nine volumes. I've included selected volumes on this slide that are most relevant to this audience. The requirements for biological products including blood and blood components are found in parts 600 through 680 as highlighted on the slide. However it's important to review and understand the various other provisions that are applicable to FDA regulation of drugs and biologics including those in parts 1 through 99 that address product recalls, administrative procedures, FDA's use of Advisory Committees and good guidance practice.

Parts 200 through 300 address drug labeling, good manufacturing practice as well as investigational in new drug applications. Part 800 is dedicated to devices. And part 1271 establishes regulations for human cells and tissue products.

Title 21 CFR sub chapter F is dedicated to biologics. Blood and blood components is biological products are subject to these regulations including the general requirements and establishment standards that are found in part 600 and licensing requirements in part 601. Several parts of this

sub chapter are specific to blood and blood components where contained subparts that are applicable only to these products.

For example, current good manufacturing practice regulations for blood and blood components are in part 606. And the GMP applications are applicable to all manufacturers bluing blood collectors and transfusion services. The requirements for blood establishment registration and product listing are in part 607. And the requirements for blood donation testing are in part 610. And part 630 are the newest regulations on blood donor eligibility and donation suitability that became effective in 2016. And finally part 640 contains additional standards for certain blood and blood products. And as a general rule or note that you must follow the most prescriptive regulation for blood and blood components when applicable.

Next I'll provide a little bit more detail with respect to each of these parts. Regulation specific to licensure of biological products are in 21 CFR part 601. Included in this part are procedures for filing a BLA; and for FDA issuance of a complete response letter. The regulations in this part also establish the standards for the issuance, denial and revocation of a license. Under 601.12, are requirements for reporting changes to an approved application to FDA. This section describes various supplement types based on the risk of the manufacturing changes to have an adverse effect on the safety, purity and potency of the product.

And FDA's requirements for products in short supply are in 601.22. And I call your attention to this requirement as it is applicable to the manufacturer and distribution of recovered plasma.

The current good manufacturing practice regulations for blood and blood components are found in part 606. And examples of requirements in this section include those related to your personnel, facilities, and equipment. This part requires that you establish, maintain, and follow standard operating procedures for all steps in the manufacturer of blood components. It sets forth the requirements for container labeling and for circular of information for components intended for transfusion. And it requires that blood establishments and transfusion services have procedures in place to control bacterial contamination of platelet products and for testing to ensure compatibility between the donor and recipient. And 606, 100 addresses recordkeeping requirements and 606.17D requires that you investigate all donor and transfusion adverse events and report fatalities to FDA. Please note that the current good manufacturing practice regulations in 21 CFR parts 210 and 211 also apply to blood manufacturers. There are more specific regulations, the more specific regulations in part 606 are intended to supplement the regulations in the 200s. However, as a general rule and as described in 211.1B, you must follow the more prescriptive regulation if there is a conflict between the two sets.

Regulations to protect the health of blood donors are found in you 21 CFR 630.10 and 630.15. This section requires a donor acknowledgment the and informed content to make sure the donor understands the risks and hazards of the blood Doe stayings procedure and has an opportunity to ask questions. To ensure the donation will not adversely affect the health of the donor, the requirements for donor questioning, for certain medical conditions and medications, physical assessment and examination, the measurement of donor hemoglobin and total protein levels before donation and limits on donation frequency and deferral for red cell loss.

Regulations to ensure the safety of the blood supply include requirements for testing blood donations in 21 CFR part 610.40. And they are specific to, specific agents for which we require testing are listed on this slide. There are requirements for storage temperature and dating periods. In 21 CFR part 610.53, you must assess donors for risk factors for RTTIs as required in part 610.30. And defer donors and notify them of the deferral and the reason for the deferral as described in part 630.40. And you must ensure each donation is suitable for release as prescribed in section 630.30.

21 CFR part 640 provides additional requirements for certain blood components including proper name and source, collection, processing, testing, and donor eligibility requirements for whole blood, red cells, platelets, plasma, cryoprecipitate and Source Plasma. And I'll pension that part 640 includes distinct requirements for Source Plasma including those for syphilis testing, total protein determination and protein electrophoresis testing, as well as restrictions on distribution and quarantine hold.

So recognizing the unique nature of blood manufacturing and FDA's regulatory oversight, under CFR 460.120. The Director CBER may issue an exemption or alternative to any requirement in sub chapter F, chapter 1 of title 21 CFR. And these are the requirements for biologics in the 600s that we just reviewed. And there are two pathways under this regulation. Under 21 CFR 610.40A, the exception or alternative procedures is issued in response to a request from an individual establishment. Both licensed and registered only establishments must make a written request to FDA. Under this regulation, the exemption granted is only applicable to the requester. And an example of a type of request that might come in might be from an establishment the that may need to request a variance to continue operations in the face of a natural disaster.

Under 61040B, CBER may issue an exemption to respond to a public health need to ensure the availability of blood or blood components or to provide for the appropriate donor screening and testing. CBER would make this determination and issue a notice describing the exception which may be broadly applicable to all blood establishments. We may issue this notice in a guidance or through a web posting, depending on the circumstances and need.

For example, we issued a guidance that provided alternative procedures to certain regulations to permit the manufacture of cold store platelets.

And finally I wanted to highlight the regulations in 21 CFR part 312 for investigational new drug applications. While not specific to blood components, the regulations in this part address when an IND is required, provides requirements for labeling of an investigational new drug, the content of an IND application, it describes the phases of an investigation, and the requirements for IND safety reporting as well as the responsibilities of investigators and sponsors. So the entire code of federal regulations is accessible electronically and maintained by the national archives. The eCFR is searchable and provides the authority or statute as we have learned. The source and history of each subpart. There are links to the Federal Register notices associated with each regulation that also provides the preambles. And reviewing the preambles can help you understand FDA's rationale for the rulemaking as well as our expectations for compliance with the regulations.

I have provided the links to the eCFR for title 21 which you now know is for food and drugs. As well as Title 42 which includes regulations enforced by CMS under the authority of CLIA that may be applicable to your establishments as laboratories.

So in this final section, I'll review guidance documents.

So while regulations have the force and affect of law, guidance documents are intended to describe an agency's interpretation of a regulation or regulatory issue or FDA's current thinking on a topic. Most guidance documents are not binding and provide FDA's recommendations to industry. The use of the word should in a guidance document indicates a recommendation. While the word must is used to denote a requirement. FDA is required to develop guidances under good guidance practice regulations in 21 CFR part 10.115. Much and these regulations ensure FDA communicates new policies through guidance documents and used established procedures for developing and issuing guidance.

For most guidances, FDA will issue a Federal Register notice, inviting public comments on a draft document. And after considering all the comments, we will issue a final document. FDA may issue a guidance for immediate implementation, however, if prior public participation is not feasible or appropriate. For example, you'll recall that we issued several guidances during the COVID-19 public health emergency for immediate implementation.

OBRR's policy development is science based and data driven. We are committed to seeking input from stakeholders when possible. We may discuss scientific considerations related to policy development with the blood products Advisory Committee where interested members of the public also have the opportunity to present their opinions and data. And on occasion we hold public workshops to gather data, information, and opinions on topics. And we consider all public comments received on guidance documents before issuing a final recommendation. And to ensure stakeholders are informed of our policy priorities, CBER post the annual guidance agenda on the FDA website. And the guidance agenda is usually updated in January, in June of each year. And list the documents we aim to publish in the current calendar year. The list is not binding on FDA but it is a good signal of our intentions and our priorities.

So we issue guidance on various topics including donor eligibility. For example, in 2023 we issued recommendations for using individual-based, individual-risk based questions to assess HIV risk in blood donors. We interpret the RTTI and donation testing regulation and guidance. In 2019, for example, we issued notice that we determined that babesiosis to be an RTTI and recommended donation testing in high risk states.

In 2019 we issued guidance that recommended strategies to control bacterial contamination of platelets under 606.145. Through guidance, we also recognize certain industry developed standards as applicable for use to comply with the regulations. For example, we recognize circular of information, container labeling standards as well as donor history questionnaires. And these documents then may be used by all blood establishments. And on occasion we issue guidance that describes FDA's intention to issue enforcement discretion to certain regulations. Most recently we issued guidance that addresses compliance with requirements for assessing a

donor's eligibility based on blood pressure and pulse measurements. And all blood guidances are housed on CBER's website at the link provided on the slide.

But please note that other FDA guidance documents may be applicable. And you should review and keep abreast of new documents.

And this is just a screenshot of CBER's current guidance agenda. Hopefully you'll be able to see it. It's dated January of 2026. And you'll see there are five documents listed for development by OBRR this year. We do anticipate updating this list in June to add additional priorities.

And on a indication, FDA may issue a safety communication to provide the public with important information about the safety and availability of biological products. So unlike guidance documents which are directed only at FDA regulated entities, safety communications may address a broader audience including healthcare providers, blood donors and consumers. The safety communications provide our considerations on an emerging safety issue. And they are not guidance documents. Recent examples of safety communications include best practices for ensuring cybersecurity in blood establishments. And considerations for reporting septic transfusion reactions and bacterial contamination of platelets to FDA.

So in conclusion, the objective of this session was to describe FDA's regulatory requirements for the manufacture of blood and blood components including Source Plasma. I explained that FDA's regulatory authority to regulate blood and blood components as biological products and drugs is derived from the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act which are laws enacted by Congress.

FDA as an executive agency, issues regulations to complete the statutes. FDA's regulations which are legally enforceable are in title 21 of the code of federal regulations and sub chapter F is dedicated to biologics which includes regulations specific to blood and blood components.

Finally FDA issues nonbinding recommendations for how to comply with the regulations and guidance documents. FDA must comply with the Administrative Procedures Act and good guidance practices to ensure public participation in the development of guidance and regulations. And we encourage your participation in this process.

So that ends my presentation. I thank you very much for your attention. And Dr. Yeowon Kim is our next presenter. And she will be discussing requirements for donation testing and donor deferral requalification and notification. Dr. Kim?

>> DR. YEOWON KIM: Good morning, everyone. My name is Yeowon Kim. And I'm a Medical Officer in CBER OBRR. Today, I'll be covering screening for relevant transfusion transmitted infections or RTTIs, donor deferral, notification and requalification.

The objective of this session is to identify testing, donor deferral and notification requirements for relevant transfusion transmitted infections or RTTIs and donor reentry recommendations.

A transfusion transmitted infection or TTI is a disease that is fatal or life threatening, can cause permanent impairment or necessitate medical or surgical intervention and is potentially transmissible by transfusion.

Relevant RTTIs are subset of TTIs that FDA considers to be the most important to the safety of the blood supply.

There were ten RTTIs names in the code federal regulations or the CFR including HIV, hepatitis B and C and the others listed here.

Testing for an RTTI is required under FDA regulations, FDA licensed approved or cleared screening test are available and testing is necessary to reuse adequately and appropriately the risk of transmission.

In addition to the ten named RTTIs and the CFR, FDA may determine that TTI is an RTTI if the TTI has sufficient incidence and prevalence in the donor population and there are appropriate screening measures available.

FDA's determination of an RTTI can change based on the available scientific information, and FDA will inform the public when an RTTI determination is named or changed.

For example, the Babesia species is an agent which FDA has determined to be an RTTI in which testing is currently required for donations collected with Babesia endemic states. Zika virus was determined by FDA to be an RTTI in 2016 and testing became required. The RTTI designation and testing requirements were withdrawn in 2021 because available evidence showed that Zika virus no longer had sufficient incidence or prevalence to affect the potential donor population.

FDA's regulation of blood safety focuses on minimizing the risk of RTTI transmission, while ensuring an adequate blood supply. Blood testing is based on multiple overlapping safeguards. These include providing educational materials that instruct donors to not donate if they have RTTI risk factors and symptoms and screening donors with a DHQ with deferral for RTTI risk factors.

Testing donations for RTTIs is critical for blood safety as many blood components for transfusion are not treated to inactivate infectious agents. Additional safeguards after screening and testing include maintaining cumulative donor deferral records to prevent ineligible individuals from donating and taking appropriate actions on post donation information.

Screening for RTTIs includes questioning donors for RTTI risk factors and performing screening tests on donations. In general, the requirement is to test every donation unless regulations and guidances state otherwise. For example, every donation is tested for HIV one and two and hepatitis B and C without exceptions. For blood and blood components, one time testing is recommended for Chagas and geographic risk based testing is recommended for Babesia.

The five RTTIs for which testing is not required for Source Plasma are west nile virus, HTLV1 and two, Chagas, Babesia, and malaria.

There are exceptions to testing for dedicated donations, some medical devices. Samples used for clinical laboratory testing or research purposes and autologous donations. Here's a table summarizing the RTTI testing requirements for blood and blood components compared to Source Plasma.

As I mentioned previously for Source Plasma, testing for west nile virus, HTLV one and two, Chagas and Babesia are not required. Additionally for Source Plasma, anti-hepatitis core antibody testing is not recommended.

FDA's frequently asked why questioning donors is required when donations are tested for RTTIs. We regard questioning as an additional safeguard against RTTI transmission. Questioning donors to confirm that they are healthy at the time of donation decreases the chance of collecting donations from a donor who may have symptoms of an RTTI. Hence, it lowers the burden of potential infectivity that must be detected. Questions also decreases the potential introduction of an infectious unit, that may be test negative during the window period or due to testing limitations such as false negatives and viral variants.

Approach to screening donors for particular RTTI depends on whether there are identifiable risk factors and available screening test for that RTTI. Both questioning and testing are used for RTTIs from which there are identifiable risk factors and available screening tests. Testing only is used when the screening test is available and there are no identifiable risk factors that can distinguish individuals of risk of infection through questioning.

Questioning only is used for RTTIs with identifiable risk factors and no available screening tests. Currently, questioning or testing issues for Babesia, approach depending whether the donation was collected in the Babesia endemic stage. I wanted to mention that FDA allows to use a pathogen reduction instead of testing for Babesia for plasma and platelet donations.

Testing or packaging reduction is required for donations collected in Babesia endemic states. When testing or pathogen reduction is performed. Questioning donors about history of babesiosis is not necessary. Low risk states that do not test for Babesia or pathogen reduced blood components should ask donors if they had a history of babesiosis.

This and the following slides outline general principles for RTTI testing. This includes using one or more screening test that FDA has licensed approved or cleared for such use in the importance of following the manufacturer's instructions. All testing that's required to be performed in a CLIA certified lab or equivalent. And all samples for testing must be properly identified and labeled.

Donations with reactive screening test must not be shipped or used unless there is an exception. Blood components may be shipped before testing is completed only if documented medical emergencies. Good manufacturing practices or GMP requirements for blood and blood components apply to RTTI testing which includes-- maintaining, and following relevant SOPs. Additionally the GMP regulations contain traceability requirements so that every unit is tracked from the donor to the final disposition of the product so that unsuitable units are not distributed.

So what muster you do when a donation tests reactive? First, do not ship or use the unit unless there is an exception. The unit must be appropriately labeled and quarantined. Second, perform further testing with a licensed, approved, or cleared supplemental test.

Third, defer and notify the donor and add the donor to your deferral registry in the deferral space in the reactive screening test even if it hasn't been confirmed by further testing.

There are some exceptions to donor deferrals for reactive screening tests which include, the donor who tests reactive or anti-HBC or anti-HTL V1 and two on only one occasion may be eligible to donate Source Plasma. Also such a donor who test reactive to anti-HBC or anti-HTLV one or two on only one occasion is not required to be deferred. However the donor must be deferred if further testing is positive.

This slide outlines requirements related to donor notification. On the day of donation, you are required to obtain proof of identity of the donor and a postal address for the donor may be contacted for eight weeks after donation. You must notify any donor deferred for reactive RTTI screening test. For not meeting eligibility criteria which includes DHQ responses and endogenous bacterial infection. Notification must include the reason for a deferral, the results of RTTI testing including further testing, and information regarding medical follow-up and counseling. The donor should be notified within eight weeks. You must not collect blood before determining that the donor is eligible. You must document successful notification or reasonable attempts.

The next set of actions relate to product management. You are required to perform lookback if a donation is reactive for HIV or HCV, the regulations have specific requirements for HIV and HCV lookback. For other RTTIs, product management recommendations are outlined in the guidances for each RTTI which may include identifying in-date blood and blood components previously donated by the donor; quarantining such units and notifying consignees to do the same; and taking appropriate action based on results of testing which include releasing, destroying and relabeling quarantined in-date blood products consistent with test results and notifying the recipient's physician if appropriate.

FDA licensed or cleared RTTI screening tests are highly sensitive and specific. However, given the volume of donations screened annually, there are many reactive donations in which the majority of false positive. For the 2023 national blood collection and utilization survey, of the 11.5 million units of whole blood and aphreresis red blood cells tested, there are 123,000 units or about 1% lost to RTTI screening. To put this in perspective, this number is small, about one seventh of that compared to the total production losses in--

So we acknowledge that this represents. Donors who are deferred who are likely false positive of RTTI screening test. Hence, FDA recommends requalification and reentry of deferred donors to maintain a robust donor pool.

A deferred donor may be found eligible for requalification method or process FDA has found to be acceptable. In addition to meeting specific reentry criteria, the donor needs to meet all other donor eligibility criteria to be able to donate in the future.

FDA guidances contain recommendations for requalification methods and reentry criteria for each RTTI. The recommendation specify what screening test results are eligible for requalification, the time interval between the index reactive test result and the testing to be performed for requalification and whether testing should be done on the follow-up sample or on a subsequent donation.

We acknowledge that not all possible screening test result scenarios are covered by the guidances. If a test result scenario for a donor is different than those addressed in the guidance, and you have evidence that the donor is not infected, we encourage you to contact us and submit an individual reentry request for us to review.

Here's an example of the most common type of donor reentry request that FDA receives. Just to reenter donor with lost historical records of a reactive screening test. In this case, the donor was initially deferred for an unconfirmed anti-HIV one and two test result and historical records were no longer available. The blood establishment used to substitute index donation sample which was non-reactive and performed testing on the follow-up sample in a manner that was consistent with the requalification method recommended in the FDA guidance.

Since the follow-up test results confirmed that the donor was not infected with HIV, FDA granted the donor reentry, provided that all donor eligibility criteria are met.

For the second part of this talk, I'll be applying the concepts that we just covered regarding RTTI screening, donor deferral, notification, look bang, requalification to HIV one and two.

This and the following slide go over donor education and questioning of donors as they pertain to HIV. Blood establishments must provide educational material to donors before each donation, explaining the risk of HIV transmission by blood and blood products and risk factors associated with HIV infection so that donors can self-defer.

The educational materials instruct potential donors to not donate if they have HIV or at risk for HIV, have ever taken medications to treat HIV or taking medications to prevent HIV or have symptoms of HIV infection. Additionally, educational materials should instruct individuals to not discontinue their prescribed medications including those taken to prevent HIV in order to donate blood.

Both questioning and testing are used for HIV screening of donors since there are identifiable risk factors and available screening test for HIV. The DHQ assesses HIV risk factors including individual risk based questions about new and multiple sexual partners, blood exposure, and medications to treat or prevent HIV infection.

Listed here are HIV risk factors that FDA recommends to be included in DHQs. Risk factors fall into three categories, behavioral risk factors, risk factors related to blood exposure and procedures associated with potential HIV exposure and history of HIV positivity or medications taken to prevent or treat HIV. The recommended deferral period depends on the risk factor.

The next several slides pertain to HIV testing of donations. Licensed donors screening tests for HIV include nucleic acid tests or NAT or HIV-1 or antibody tests for antibodies to both HIV 1 and 2. HIV NAT is typically performed using many pools of six to 12 samples in the multiplex with HPV and HCB nucleic acid testing. Additionally there are multiple licensed supplemental test for further or confirmatory testing.

The importance of using both questioning and testing to screen donors for HIV and the use of more than one screening test is illustrated by this FDA safety communication that was issued in

2019. It was brought to FDA's attention that there are a small number of HIV positive individuals on anti-retroviral treatment who donate blood and are found reactive onscreening tests. Although individuals with HIV who maintain an undetectable viral load on conventional testing cannot sexually transmit HIV to others, this does not apply to transfusion transmission due to the large volume of blood involved.

While HIV viral loads of individuals on anti-retrovirals may be under the limit of detection by nucleic acid testing, antibody testing may still be positive. Additionally, DHQs include questions regarding history of HIV positivity and medications taken to prevent or treat HIV.

Here are the regulations relevant to HIV testing for blood, blood components, and Source Plasma. Each donation must be tested for HIV using licensed screening tests. For HIV, both NAT and antibody tests must be used to reduce adequately and appropriately the risk of HIV transmission. Donations that are reactive onscreening test must be further tested using licensed supplemental test. This requirement for further testing includes autologous donations. You may release donations as non-reactive on HIV screening tests, provide that all other donations suitability requirements are met. If a donation is reactive on an HIV screening test, you must not release the unit and defer and notify the donor. FDA encourages to requalification and reentry of deferred donors who are eligible for requalification.

A common question that FDA receives is whether a blood establishment can release a donation that was initially reactive for HIV or another RTTI if results of further testing are negative. And the answer is no. Reactive donations must not be shipped or used unless there is an exception. If further testing is negative on the reactive donation, prior donations involves in lookback or product management for other RTTIs may be released. Similarly, blood establishments must defer donor with the reactive HIV screening test even if further testing is negative. The results of both the screening test and further testing will factor whether a donor is eligible for requalification.

The good news is that the residual risk of HIV is very low and is declining. The transfusion transmissible infections monitoring system or TIMS calculate the residual risk of HIV transmission by transfusion in the U.S. to be approximately one in it 4.4 million units.

The estimated window unit for HIV which is a time period between the initial infection and when a diagnostic test can reliably detect that infection with NAT testing is 9.1 days.

This graph illustrates the importance of using more than one screening test. Early in infection, NAT may be positive while antibodies are negative. Later in the course of infection, the viral load may decrease but antibody in manufacture, IGG may be positive.

As I mentioned earlier, lookback is required if a donation is reactive for HIV or HCV, the regulations have specific requirements for HIV and HCV lookback. The requirements for HIV lookback are under title 21 CFR part 610.46.

The regulation specified that for HIV lookback within three calendar days after donor test reactive for evidence of HIV infection, records must be reviewed to identify blood and blood components previously donated by the donor.

The blood components involved in lookback are those that were collected 12 months and less before the donor's most recent non-reactive screening test or 12 months and less before the donor's reactive nucleic acid test and non-reactive antibody screening test whichever is the lesser period. The latter test results indicate early HIV infection prior to the generation of antibodies.

For blood components involved in lookback, blood centers must quarantine all previously collected in-date units except for pulled units intended for manufacturing into products using validated viral clearance procedures.

Blood centers must also perform further testing for HIV on the reactive donation. If further testing is positive, quarantine units must be relabeled or destroyed. Blood centers must also notify consignees so they can take appropriate actions the which includes notifying transmission recipients or their physicians.

Last few slides address donor requalification and reentry after reactive HIV screening test. A common question that FDA receives is whether a blood establishment can requalify a donor with a false reactive screening test result for HIV. And the answer is yes, provided that the donor's eligible for requalification and the results of follow-up testing support that the donor was never infected with HIV.

This table illustrates HIV screening test result scenarios that would not be eligible for requalification. Each row represented a set of HIV screening test results for an individual donor. I wanted to mention that P24 antigen testing is no longer recommended by FDA as a screening test for HIV. What's included in this table is a deferred donor space in historical P24 antigen testing results. You can see that each row on this table has more than one reactive test highlighted in red which is supported of HIV infection hence donors with these screening test results would not be eligible for requalification and should be permanently deferred.

By contrast this this table illustrates HIV screening test result scenarios that would be eligible for requalification. Similar to the last table, each row on this table also represents a set of HIV screening test results for an individual donor. You can see that here each row has only one reactive test which is likely to be a false positive as the reactive test result is not supported by the results of other tests.

Hence, donors with these screening test results would be eligible for requalification.

To requalify deferred donor with a likely false positive HIV screening test, a follow-up sample should be obtained and tested for individual HIV NAT and anti-HIV one and two screening test at least eight weeks after the reactive test result.

If both tests are negative, the donor can be reentered as eligible for future donation provided they meet all other eligibility criteria.

In closing, the multilayered approach to blood safety has resulted in historically safe blood supply with residual risk of many RTTIs being very low and declining. Although FDA licensed cleared RTTI screening tests are highly sensitive and specific, we acknowledge that there are many donors who are deferred for likely false positive screening results. FDA recommends

donor reentry to maintain a robust donor pool and highlight our guidances which include requalification recommendations for each RTTI.

FDA continues to monitor emerging transfusion transmitted infections and refine RTTI requirements and recommendations based on current science. We encourage you to check regularly the FDA blood guidance's web page and biologic safety and availability communications to stay informed on current recommendations and emerging safety concerns.

This is the end of my presentation. Thank you for your attention. And at this time, I would like to introduce our next speaker, Carmelita Bibby who will be covering blood establishment registration and facility relocations.

>> CARMELITA BIBBY: Good morning. My name is Carmelita Bibby and I am a Consumer Safety Officer with the Office of Blood Research and Review.

Today, I'll be walking you through the regulatory requirements for blood establishment, registration, and what facilities need to know when undergoing relocations, acquisitions, or mergers. Let's get into it.

My portion of today's presentation will focus specifically on objective two, the requirements and process for blood establishment the registration. This includes who must register, when and how to register, what information is required, and how to handle facility changes such as relocations, acquisitions, and mergers.

So why does FDA require blood establishments to register in the first place? There are three core reasons. First, registration allows FDA to maintain accurate information and track manufacturing facilities and the products they produce. Second, it helps FDA identify and locate facilities for inspections which is critical to ensuring product safety and compliance. third and perhaps most importantly from a public health standpoint, registration improves FDA's ability to respond quickly and effectively to public health emergencies.

Knowing where facilities are and what they've produced is essential when time is of the essence.

The primary regulatory framework governing blood establishment registration and product listing is found in 21 CFR part 607. Within in part, section 607.3 provide the key definitions you'll need to be familiar with. Specifically it defines what constitutes a blood and blood product understand 607.3B, what qualifies as an establishment under 603.3C and what activities fall under the definition of manufacture under 607.3d, understanding these definitions is foundational. Because they determine whether your facility is subject to registration requirements in the first place.

Registration is required for all owners or operators of establishments that engage in the manufacturing of blood products. If you are a manufacturing product blood products intended for commercial distribution, you must list all of those products. Importantly, registration must occur before a biologics license application is submitted. You cannot submit a BLA without first being registered.

One thing worth noting, there is no registration fee for blood product registration and listing which removes a potential barrier for facilities.

Timing matters when it comes to registration. Under 21 CFR 607.21, a blood establishment must register within five days after beginning operations or within five days after submitting a BLA, whichever comes first.

In addition, all establishments must reregister annually between October 1 and December 31. Blood product listings must also be updated every June and December to reflect any changes in the products being manufactured or distributed. These are firm deadlines. So it's important to build them into your facility's compliance calendar.

This is an important distinction that sometimes causes confusion. Registration alone does not authorize a blood establishment to ship blood products across state lines. That is interstate commerce.

To distribute blood products in interstate commerce, a facility must have an active biologics license. That said, a facility can be registered without holding a biologics license. In that case, the establishment may operate and distribute blood and blood components within the state only. So registration and licensure serve different purposes and confer different authorities.

Who is exempt from registration? Not every entity involved with blood products is required to register. Under 21 CFR 607.65, there are several categories of exemptions. Pharmacies that are not manufacturing blood products for sale are exempt. Manufacturers of blood products that are not for sale and are used solely for research, teaching or analysis are also exempt.

Additionally, persons who engage solely in the manufacturing of in vitro diagnostic blood products and reagents that are not subject to licensing under section 351 of the Public Health Service Act are exempt from registration.

Continuing with exemptions, transfusion services that do not collector process blood and blood components and are certified under the Clinical Laboratory Improvement Amends Act of 1988 are also exempt. Some practical examples of activities that are exempt from registration including compatibility testing, preparing red blood cells for transfusion, and pooling certain blood components before transfusion. these are considered lower risk or routine clinical activities that do not rise to the level of manufacturing, requiring registration.

This slide is designed to help transfusion services quickly determine whether they need to register. The answer depends on the specific activities being performed. Activities that do require registration include irradiation, washing, prestorage pooling, freezing, deglycerolization, and rejuvenation of blood components. Extending platelet expiration after bacterial testing and acting as a depot that routinely stores and ships products to other hospitals. Activities that do not require registration include compatibility testing, preparing blood components for transfusion, pooling certain blood components before transfusion and collecting and processing blood and blood components only in emergencies.

If you're unsure where your activities fall, I encourage you to reach out to FDA directly, using the contact information we'll share at the end of the presentation.

All registrations are submitted electronically blue the electronic blood establishment the registration product and list application known as eBER. The URL for the eBER system is listed on this slide. I'd encourage you to bookmark the link if you haven't already. Electronic submissions streamlines the process and ensures that FDA receives accurate and timely information. Paper submissions are not accepted for this process.

When submitting a registration through eBER, you'll need to provide several key pieces of information as outlined in 21 CFR 607.25. This includes the facility's legal name, address, and phone number as well as the unique facility identifier which we'll discuss on the next slide.

You'll also need to specify the establishment type and identify reporting official who is the person designated by the entity to correspond with FDA. Finally, you must provide a list of blood products and the processing or manufacturing activities associated with them.

If you are registering for the first time, you will need to obtain a data universal numbering system number commonly known as a DUNS number which serves as your unique facility identifier. The DUNS number is issued by Dun & Bradstreet. And the link to apply is provided here. This number is the standard business identifier used across many federal regulatory systems. So if your organization already has one, you can use it for your blood establishment registration.

Once you submit a new registration, here's what happens on the FDA's end. The FDA official establishment inventory coordinator will contact the reporting official listed in your registration.

FDA will then assign an FDA establishment identifier number or FEI number which serves as your registration number. And the registration will be made active. FDA will then provide the FEI number and a registration summary report back to the reporting official. Keep this information on file as you'll need the FEI number for future correspondence and submissions with the FDA.

Facilities are not static. They change over time, and FDA needs to be kept informed. Under one CFR 607.26, any changes to your registration must be submitted as amendments within five calendar days of the change. Changes that require an update include a legal name change due to a change in ownership corporate structure or a partnership, a relocation or address change, a change in the reporting official, and any change in blood product handling activities such as implementing or ceasing certain processing or manufacturing activities. Five calendar days is a short window. So it's important to have a process in place to notify FDA promptly when changes occur.

In addition to the changes covered on the previous slide, facilities must also update their product listing whenever they introduce or discontinue the manufacture of specific blood products. As required under 21 CFR 607.21. These listing of dates should be submitted during the June to December update windows. Keeping your product listing current ensures that FDA has an accurate picture of what your facility is producing and distributing.

If you look up your facility in FDA's system and see a status of inactive, it's important to understand what that means.

There are three possible reasons for inactive status. Inactive closed means the establishment is out of business or has been acquired by another company.

Inactive temporary means the facility is temporarily closed perhaps due to repairs, relocation, or damage from an extreme weather event or a disaster such as a hurricane or earthquake. Inactive exempt means the establishment has been deemed exempt from registration under the criteria in 21 CFR 607.65, if you believe your facility status is incorrect, contact FDA to resolve the discrepancy.

This slide gives you a snap shot of the current landscape of registered and licensed blood establishments as of April 2026. There are 726 registered only establishments which include hospital, blood banks and transfusion services.

There are 1,000 license blood collection establishments held by 71 license holders. And there are 1204 licensed Source Plasma establishments held by 28 licensed holders.

These numbers reflect the scale and diversity of the blood establishment community that FDA oversees and underscores the importance of a robust registration system.

Now we'll shift our focus to a topic that many facilities encounter at some point in their life cycle. Facility changes. Whether your establishment is relocating, being acquired, voluntarily revoking its license or merging with another entity, there are specific regulatory steps that must be followed. The next several slides will walk through each of these scenarios in detail.

When a blood establishment relocates to a new address, note thought this constitutes a change to the registration and must be reported to FDA within five calendar days of the move as required under 21 CFR 607.26. For licensed establishments, a relocation may also trigger the need to notify FDA and potentially submit changes to the biologics license depending on the nature and scope of the move. facilities should contact FDA proactively to determine what additional steps may be required to ensure continued compliance and uninterrupted operations. If you are completely relocating but currently registered facility and moving all equipment, manufacturing activities, and staff to a new location, the current facilities registration or FEI number and compliance history will be transferred to the new location.

If you plan to move some manufacturing activities to a new facility location while keeping the current location, the new facility will need a new FEI number. Contact the FDA blood establishment registration coordinator before implementing the move. This relocation may affect the compliance history as the approvals, licensure of the current facility do not transfer to the new facility if a new FEI number is assigned.

When a blood establishment relocates to a new address -- I'm sorry. Excuse me. I did this one.

When a blood establishment is acquired, the new owners must amend the establishment registration within five days of the change of ownership. This is a firm requirement and should be part of any acquisition planning process. Additionally, if the required establishment holds a

biologics license, the new owner to contact FDA to determine whether a new biologics license should be issued to the new legal entity. Voluntary revocations where a license holder chooses to relinquish their license, also require coordination with FDA to ensure the process is handled properly and that public health is not disrupted. Please note the second bullet applies to when an unlicensed buyer acquires an existing licensed facility.

A merger involves the union of two or more establishments to form a new legal entity. Like acquisitions and relocations, mergers require an update to the registration. When applicable, FDA will issue a new license number to the newly formed entity. For detailed guidance on how to handle changes to an approved application in the context of mergers and other facility changes, I'd refer you to the FDA final guidance from December 2014, changes to an approved application, biological products, human blood and blood components intended for transfusion or for further manufacture. That guidance document is an essential reference for navigating these complex situations.

Let's recap the key takeaways from my presentation. Blood establishments must register with FDA and list all blood products in commercial distribution. Certain types of establishments are exempt from registration as we discussed. All registrations are submitted electronically through the eBER system. Facility moves, acquisitions, and mergers all require updates to the registration or the issuance of a new registration number. And if you have any questions about any of this, please don't hesitate to reach out to FDA directly at the the address listed on this slide.

For more information on blood establishment registration, I encourage you to visit FDA's CBER blood establishment registration and product listing web page, the URL which is listed on this slide. That page contains regulatory references, guidance documents, and additional resources to help you navigate the registration process. For specific inquiries, you can send an email directly to the inbox address shown here.

And now we'll pause for a break. Please return at 11:00 o'clock for part 2 of the webinar.

>> Review of the public webinar, FDA review of biologics, license applications for blood and Source Plasma. I hope you enjoyed the break. And for you who may just be joining us, just to give a little recap of part one, you heard three very excellent presentations, the first on the regulatory framework for why we do what we do and how we accomplish our regulatory goals by Jennifer Scharpf. The second one was a scientific rationale for the requirements applied in our approach to risk reduction for RTTI for Dr. Yeowon Kim. And the final was a concise presentation on the why, when, and how to register with FDA.

And all of these talks were filled with resources and practical examples of what is needed or required for you if you collect, manufacture or distribute blood, blood components and Source Plasma. Building on those foundational blocks, we're moving onto part two which is the process of BLA submissions.

And with that, I introduce your first speaker, Miriam Montes who is the branch chief for the blood and plasma branch. Thank you.

>> MIRIAM MONTES: Good morning, everyone. My name is Miriam Montes. And I am the chief of the blood and plasma branch in the Office of Blood Research and Review here in CBER.

For today's topic, I want to be calling submitting a biologics license application for blood and blood components or Source Plasma.

Our objective today is to describe the steps in submitting a biologic license application for blood and blood components or Source Plasma. My goal is to give you a clear roadmap for submitting a complete BLA. So let's begin.

Let's start with the foundation. What is a BLA? A BLA is your formal request to FDA for permission to manufacture and distribute a biologic product in interstate commerce. This is the foundation of everything that we are going to talk about today.

The BLA is how you get permission to operate and everything in your submission needs to support that demonstration of safety, purity, and potency.

Now that we understand what a BLA is, let's clarify an important distinction. Let's clarify when do you need to submit an original BLA versus when do you submit a BLA supplement?

You submit an original BLA when you are a new entity with no existing U.S. license number, and you are requesting your first biologics license. This requires a pre-license inspection or PLI. And upon approval, FDA issues a new U.S. license number.

Think of this as your first time application. You are starting from scratch. A BLA supplement on the other hand is when you are an existing, you have an existing U.S. license number and want to make changes. This includes adding a new facility which will require a pre-approval inspection or a PI, making manufacturing changes to approve operations, or manufacturing additional blood components at existing facilities. . The bottom line, a new entity with no license, you need to submit, if you're a new entity without a license you need to submit an original BLA. If you're a licensed facility and making changes you need to submit a BLA supplement.

Now that you understand the difference between original BLA and supplements, let's talk about the different types of supplements because not all supplements are created equal, they are classified based on the potential impact of the change on product safety and effectiveness.

Think of this like a traffic light system. At the top of the scale we have prior approval supplement. Those are the changes that have a substantial potential to adversely affect safety or effectiveness of the product. This is your red light which means stop. You must wait for FDA approval before you can distribute any product made using this change. Moving down the scale, we have changes with moderate potential to affect product safety or effectiveness.

Here we have two types the changes been affected in 30 days, and changes being affected CBE.

So the CBE30, you must submit at least 30 days before distributing the product, made using the change. And for CBE, you can implement immediately after FDA receives your supplement. This is your yellow light which means proceed with caution. Proceed with caution means that at

any point during the review, if there are any unresolved issues, FDA can ask you to cease distribution of the product using the change until the issues are resolved.

Now, at the bottom of the scale, we have the annual report. These are changes with minimal potential to adversely affect the product safety and effectiveness. This is your green light, meaning, you can go ahead. There's no pre-approval required, and you can submit this report annually.

Here are some examples of supplements. For prior approval supplements, if you're implementing a new immunization program, if you're implementing a new vaccine program, you will require to submit a PAS. For changes being affected in 30 days, implementation of a new manufacturing process such as leukoreduction of blood components, aphreresis affected briefly approved under a comparability protocol and my colleague will be discussing comparability protocols in details in the next topic. For changes being affected, the use of an FDA registered contract facility that currently performs manufacturing steps on blood products, for example, the implementation of a testing laboratory.

The annual report. This includes implementation of infectious disease test required or recommended by FDA, if directed by the relevant guidance document to report implementation in the annual report. Other examples include minor changes to SOPs, administrative changes.

If you want more details on supplement times and how to determine which category your change falls into, you can take a look at the 2014 guidance for industry. And we have included the link right here on this slide.

When should you submit your BLA? That is really a great question. And the answer is, not as soon as you caught the (?) in your new facility. First things first. Registration must happen within five days after beginning operations or within five days of after submitting the BLA.

So your facility must be registered. Before you even think about submitting, your operations must be established. And by established, we mean three specific things. First, your manufacturing has started, meaning you're making a product. Second, your personnel have been trained, meaning, your staff needs to know what they're doing. They need to be confident and actually performing their jobs because here's the thing. We're going to inspection your facility. And if your staff looks like us like deer in the headlights when we ask about procedures, that can be a problem.

Third, your operations and processes must be validated, and all operations compliant. Meaning your processes need to work and work consistently. Now, here's where I'm going to give you the best advice of this entire presentation. Or original BLAs, we highly encourage you to contact us, contact CBER or OBRR before you submit. Why? Because then sures you know exactly what we need and helps you submit a complete BLA the first time.

Once we receive your submission, we will sends you a request for information which is necessary for the inspection. This is facility specific information that will-- I will be discussing later in the presentation. Now, as a note, most Source Plasma centers currently operating under

an existing license, they already have these documents and usually submit them-- they've requested information with the supplement.

So let's talk about what you actually need to submit for your BLA to be filed. First, you have your form FDA 356h, this form must be signed by your authorized official. And it will include here on this slide if you need to download it. This form is critical because the information you provide particularly the product name, determines how BLA gets routed. It ensures your submission gets to the appropriate division for processing.

So be very accurate and be specific when completing this form. Second, the form FDA 2830 this is your blood establishment registration and product listing. You have to make sure your facility is properly registered and listed. Third, you need to submit sufficient information about your manufacturing process, consistent with applicable regulatory requirements. what does sufficient mean? It means you have enough information for us to understand your processes and to be able to evaluate compliance. This includes the SOPs, validation-- and processes description where you show us compliance.

So here's a partial view of the form FDA 356h highlighting some of the important sections for BLA supplements. Of course, you're going to check your committing a biologics license application. You're going to check on the BLA section, check 351a which is for blood and blood components or Source Plasma under the Public Health Service Act. Your submission time, are you submitting an original BLA? A laboring supplement or annual report or CNC?

You will also select the appropriate submission category. Is it a CBE? A CB30? Other important sections that are not shown here on the form include your applicant information, the product name. Remember, this determines the routing. So be specific. Your facility information and authorized official signature.

Here's an example of the form FDA 2830. This is about establishment registration and product listing form. This form serves two purposes. It registers your facility with FDA, and it lists the products your manufacturing. On the form, you will have your establishment information section, the registration number field, your product listing section, and the responsible official section.

The cover letter this is your introduction to your BLA and it is important. This is our roadmap to understanding what you are submitting. The cover letter must be dated and signed by your authorized official and include legal name, your legal name and address, who are you and where are you located? And you need to make sure this matches what's on your form FDA 356h. The facility requesting approval. The address and registration number of the specific facility you are requesting approval for. The summary of your request, why are you submitting this? What are you asking for? Be specific. The BLA content summary, a table of contents is preferred because it tells us what's in your submission and where to find it. It will organize table of contents really helps navigate your submission efficiently. Product names and manufacturing methods. What products are you making and how are you making them?

be specific about these products. And provide clear subscriptions of your manufacturing methods. For blood centers, you also need to submit the blood product validation plan and summary of validation results and the blood product quality control data for two consecutive months. This demonstrates that your products and manufacture consistently. You should also include adequate information, describing your sampling plan.

Your standard operating procedures, please, please, please-- submit only the ones that are relevant to your supplement. Don't send us every SOP you have ever written. Send us the one that matters for this BLA. Labeling, if you have not been previously approved to manufacture the product or if there are any changes to the container labels, you need to include them in your submissions. Your product instructions, make sure your operating instructions are consistent with what is specified in the package insert because what's in the package insert must match what you actually do. For equipment validation, all three are required, installation qualification, meaning we install it right. We need to see proof that the equipment was installed correctly. Your operational qualification or OQ means it works. It turns on. Alarm sounds when they need to sound. In other words, the equipment operates. Your performances qualification or PQ. It means your equipment works consistently and as intended under actual operating conditions. This is a critical one because it is proof that your equipment performs correctly when you are actually using it.

Now, if you're submitting an original BLA, this is for original BLAs-- you need to submit relevant SOPs that demonstrate you are compliant with regulations. Since you are a new entity, we need to see that you have comprehensive procedures in place for all critical operations. Let's start with the first category, your medical oversight which includes medical supervision and physician substitute program.

This is applicable for Source Plasma centers. Your SOPs should or must describe the roles and responsibilities of both your responsible physician and your physician substitute, including which activities the responsible physician will delegate to the physician substitute.

You need to be specific about who can do what and under what circumstances. Your serum protein electrophoresis and syphilis testing and medical review. This is required under 21 CFR 640.65B. Your SOPs must describe the evaluation of the donor serum protein results, composition if it's not within normal limits. This includes the medical review process and the statement procedures for when the donor's protein composition returns to acceptable levels. The responsible physician must review abnormal results and make medical determinations about donor eligibility. Your donor eligibility and requalification, this covers your entire process for managing donors from initial selection through requalification.

Donor selection and registration, how do you select donors and how do you register them initially? Your donor screening, your procedures for determining donor eligibility and donation suitability. You must include adequate information on your screening process, the criteria you use and how you make eligibility determinations. Donor acknowledgment and informed consent, they are two critical components here. First, the donor acknowledgment must be

documented and administered before each donation. Your SOP should describe how this is done and documented.

The acknowledgment must not contain exculpatory language, meaning you cannot have donors waive their right or release you from liability.

Second, your informed consent must include information regarding the risks and hazards of the donation procedure. Donors need to understand what they're consenting to including potential risks. Donor physical examination process or Source Plasma centers, these are procedures on how you conduct your physical examinations. Donor reentry, your procedures for how you defer donors and how deferred donors can return to donation, including the evaluation process and criteria for reinstatement.

Moving onto collection procedures. These are the SOPs that describe how you actually collect products safely and properly.

Your arm preparation, your procedures for preparing the donor's arm before collection. This is critical for preventing bacterial contamination. Your SOP should describe the antiseptic used, the technique for cleaning the arm, the area to be prepped, and how you verify proper preparation.

Proper arm preparation is one of the most important step for ensuring product sterility. For your blood product collection and management, your procedures for actually collecting and handling blood products, including the collection process itself, how you manage the product during and after collection, your SOPs need to describe entire process from puncture to product storage.

Sample collection and testing for relevant transfusion transmitted infections, your RTTIs. Your procedures for collecting samples and testing for the RTTIs. This includes which samples you collect, when you collect them, how you handle them, what test do you perform, and how you manage the results.

This is critical for product safety. Your red blood cell loss management. For plasma apheresis procedures, your SOPs for managing red blood cell loss, this is important for donor safety. You need procedures to monitor and manage the RBC laws to prevent adverse effects on donors. This group of SOPs demonstrate that you know how to collect product safely, protect the donors, and ensure proper product quality. These are fundamental for your operations.

The next category is your donor management counseling and notification. This SOPs cover how you handle problems when they arise and how you communicate with donors and-- for donor adverse events, your procedures for identifying, managing, and documenting donor adverse reaction. This includes how you classify reactions, how you respond to them, what immediate care you provide, and how you document everything. You need clear procedures for recognizing adverse events and responding appropriately to protect the donor.

Fatality reporting. Your procedures for reporting fatalities to FDA. This is critical. If a donor dies in connection with a donation, you must have procedures for immediate reporting to FDA,

investigation, and documentation. We need to see that you have clear protocols for this worst case scenario, even though we hope you never need to use them.

Donor deferral, notification, and counseling, your procedures for deferring donors for notifying them of the deferral, and providing appropriate counseling. This includes when and why donors are deferred, how you notify them, what information you provide, how quickly you notify them, and what counseling you provide. Donors have the right to know why they have been deferred and what it means for them.

Lookback and consignee notification. Your procedures for conducting lookback, when you discover information after donation that affects the product as suitability. This is critical for product safety and for public health. Your SOPs must describe how you identify affected donors, products, how you notify consignee, what information you provide and you how you track the process to ensure all appropriate parties are notified.

This group of SOPs demonstrate handle adverse situations, communicate appropriately with donors and protect public health through proper notification. Moving onto product management, equipment, and supplies. These SOPs cover how you manage your product and maintain your equipment. You need to have procedures for labeling products correctly. This is critical for safety. Labeling errors can clause fatal, incompatible transfusions. You need to describe your labeling process, and how you control the process to prevent errors and mix ups.

Source Plasma quarantine hold, procedures for quarantining plasma until the 45 day hold is completed and the donor has been qualified. What are your release procedures to ensure there is no premature release? Source Plasma and frequent donation, procedures for managing frequent plasma donors. Your donation frequently, monitoring medical oversight. Your equipment and prize which include calibration and maintenance. This includes your calibration schedules, preventive maintenance, documentation. Improperly maintained equipment, that can malfunction can cause donor injury or product quality issues. Your storage and release of critical supplies. You need procedures for storing and release of critical supplies. You need procedures for storing and releasing critical supplies such as your collection bags, anti-coagulant, reagents. How do you store properly? How do you verify acceptability before use? How do you check for damage? you need to have a control of release to ensure only acceptable supplies are used. This group of SOPs show you manage product safely and maintain equipment and control of supplies.

The final category of SOPs, issue quality systems. This is where you show us you can maintain quality operations. Quality assurance program is your systemic approach to ensuring quality throughout your operations.

Your SOP should describe your instructor, who is responsible for quality oversight, how quality is monitored. Management review process and how you ensure continued compliance with regulations. This is your overarching quality framework. Management of deviations and internal assessments, your procedures for identifying, documenting, investigating, and managing deviations. This includes how you classify deviations, how you invest the root causes, and how you implement corrective and preventive actions, and how you conduct internal assessment to identify potential issues before they become problems.

Your document management, your procedures for controlling documents, this includes how you create, review, approve, distribute, and revise documents like your SOPs. You need document control to ensure everyone is using current approved procedures and that out of date documents are removed from use.

Your procedures for investigating failures and reporting biologic product deviations to FDA. Your SOPs must describe when BPERs are required, how you investigate, and how do you report? Your downtime procedures, your procedures for what happens when the systems go down. The computer crash, the power goes out. Your SOP must describe how you continue operations safely during the downtime, how you manage product safety and traceability, and how you document everything that happens during the downtime.

These comprehensive SOPs demonstrate you have procedures for all clinical operations and quality systems. Right now you have all your information together.

You are ready to submit. Now what happens? How do you actually get the BLA to us? You have two electronic options, option number one is the electronic submissions gateway or the ESG. This is FDA's official submission system. It's a secure system, and it is the government's official portal for regulatory submissions.

To set up an ESG account, you can go to the link on this slide, follow the instructions, create your account. And then you can submit your BLA electronically through the gateway

The second option is to email. You can also submit via email to the FDA document control center. So the process is simple. You have all your documents ready to go. You can submit either via ESG or email. And it gets to us here at the FDA.

Now, CBER strongly encourages to use secure email for all the BLA communications. Why? Because you're sending sensitive information, facility data operations, donor information. So the secure email encrypts your information and protects your sensitive data. However, if you don't have secure email, we will send a notification with two options. You authorize us to communicate with you via a nonsecure email or you can set up a secure email account. And I provided a link in there on how to set up the account for secure email.

Okay. So you'll hit submit. Congratulations. Now what happens?

First stop is the document control center or DCC. This is the FDA's center of receiving and processing unit for electronic submissions. When you submit, DCC receives your submission, processes, validates the submission, loads it into the specific electronic system. You get assigned a submission tracking number, also known as STN. Your STN is important because this is your application identification number. Everything from here out, reference is going to reference this STN.

After that, DCC routes your submission to OBRR. And it gets assigned to a regulatory health project manager also known as RHPM.

Please note that your application is going to get routed based on the product you reported on the form FDA 356h. This is why I emphasized earlier that you need to be accurate and specific on

that form. If you included the wrong product name or something that is not clear, your BLA might get routed to the wrong office, and this can cause significant delays in the review process.

So now you have an RHPM assigned. Now the team continues to build. The RHPM sends your submission to our blood and plasma branch team leads and says, we need a reviewer for this submission. The team leads assign a consumer safety officer or a CSO to be your product reviewer. The CSO is then added to the review committee.

So here's the complete flow from submission to full assignment. DCC receipts, assign an STN number, sends it to OBRR. And the RHPM is assigned and sends it to BPB for assignment to a CSO.

So now, you have a review team assigned. What do these people actually do? Let's talk about what they are and their roles.

The RHPM or regulatory health management is exactly what the title says, they manage the regulatory review process, specifically, they manage the overall review process with timelines for completion of regulatory and administrative actions. They schedule and coordinate with your committee meetings and handle all the communications related to your application. In other words, the RHPM is your main point of contact throughout this entire process.

The CSO is your subject matter expert. They're your technical experts. This is the person who actually goes into BLA and does the detail technical review. The CSO reviews all components of your submission, completes the appropriate documentation, creates review memos, document their assessment and participates in review committee meetings.

Now, that you know who is on your team, let's talk about what happens next. Okay, so you submitted BLA. It's been received. You have the review team. You are going to get an acknowledgment letter from your RHPM let's walk quickly what's in the letter.

You have your submission information which includes the date you submitted, the date we received it, the reason for the submission, the license number, and the supplement type. It also includes a timeline which includes a target goal. This target goal is only based of on availability of resources. Filing decision timeline, typically within 60 days of receiving your submission. It includes information on administrative requirements such as your STN which you will use on all future correspondence. It also provides instructions for submitting additional information. It includes important clarification, indicating that acknowledgment is not approval. Or what we-- or what we have received in the submission has been evaluated.

Contact information, it has the name, phone number, and email of the RHPM. When you receive that acknowledgment letter, that is good news because it means you're officially in the system, and the process is moving forward.

However, if it's been more than two weeks, and you haven't heard from us, please contact us. The electronic systems are not perfect. And sometimes, believe it or not, submissions don't make it through for reasons we cannot explain. So please follow-up if it you have not received your acknowledgment letter within at least two weeks.

So you submitted. You have a team. You have been acknowledged. Now what actually happens?

The CSO conducts what we call a filing review. This is a preliminary look at your submission. And the CSO is asking three key questions. Is the number requirement information here? Can we actually conduct a review? Are there any major problems that would prevent us from filing this submission? There are three possible outcomes. Everything looks good. So that's great. We file your BLA and move forward with the meaningful review.

The second option could be there are some deficiencies but there's nothing major. That's okay. We'll communicate with you those deficiencies and try to work toward a resolution.

Or it could be a major problem. This is where we can refuse to file your submission. It is our way of saying, we cannot review this because it is too incomplete.

The refuse to file is actually trying to help you because instead of spending months reviewing an incomplete information, only to tell you in the end that critical information is missing, we're telling you upfront. It is telling you fix it and come back with a complete submission.

Why does FDA conduct filing reviews? Filing reviews are regulatory tool to determine if an application is complete enough to review. There are three reasons, if critical information is missing, we spend time reviewing only to realize we can make a decision. Then there are analyst cycles of review and incomplete submissions asking for missing information, reviewing again, and again which makes the process very inefficient.

So we tell you early in the process and give you the opportunity to fix the problems and resubmit a complete application.

So what actually causes an RTF? There are three main reasons, administrative incompleteness. You're missing required information, entire sections, SOPs, validation, Q C.

Scientific incompleteness, you're missing critical data or information we need to evaluate the safety, purity and potency of the product.

Inadequate content, presentation, organization: The information is presented in a way that we literally cannot review or can read it or can understand it. It's complete chaos. And we don't even know where to start. Please note that the issuance of a refuse to file letter does not happen very often. We do try to work with you to resolve the discrepancies before the filing target day.

So what does filing mean? It means that you have provided sufficient information to permit a meaningful review. So we have the minimum information required, and we will conduct a comprehensive review. Translation: It means enough here to work, let's review it. However, filing does not mean that a license has been issued or will be issued. It doesn't mean your submission is approved, that the data has been evaluated for adequacy of quality, that your facility or the product meets all requirements. Translation: We haven't graded your homework. We're just confirming you turned it in. For original BLAs, however, in addition to the acknowledgment letter, they receive a separate filing letter. After the CSO's complete, they file a review, and this is approximately 60 days after we receive your submission. For BLA

supplement, you will not receive a separate filing letter. You will get the acknowledgment letter. Now the acknowledgment letter indicates if you don't hear from us within 60 days, you can consider your submission filed.

So when you get filing confirmation, sure, you can celebrate a little bit because that means you submitted a complete submission. However, don't celebrate too much because the review hasn't even started yet. The real work begins after filings. That's when the CSO actually looks at your data, evaluates your processes, and determines if you meet requirements. So filing is just the starting line, not the finish line.

So what happens next? There are two paths. Path number one, your submission was successfully filed. This is the happy path. The CSOs are looking into your BLA. They're reviewing your data, evaluating your processes. They might request additional information, this is where the CSO also will schedule your pre-license or pre-approval inspection. And you will internet at least 30 days advanced notice before we show up.

And then we have path number two. Your submission is not filed. This is the less happy path which means we can't review this because critical information is missing. We send you an RTF letter, explaining exactly what's wrong. And you must fix it and resubmit. But you just don't submit the corrections. You submit the entire BLA. And you will also have a new STN number assigned.

For facilities, we require an inspection. OBRR is going to request additional information and data for review to support the inspections. This is the facility specific information request I mentioned earlier. And it's tailored to your facility type.

Now, here's the golden rule. Your facility to be operational for a minimum of three months before you submit your BLA. It's not three weeks. It's not one month, it's not two and a half months. It's three months. Why? Why three months? Because we need to see that you can maintain consistent operations over time.

Now, when we request additional information for the inspection, the data timeframe that we request differs depending on your facility. Source Plasma centers typically submit shortly after opening. So we request data since opening which is usually about three months. Blood centers on the other hand, are usually operational longer before submitting supplements. So we request data for the last six months to capture more historical operational data.

We're going to send a self-assessment form requesting the information. And this form must be signed completed, dated and signed by your authorized official. This authorized official's signature attest to the completeness and accuracy of all the information submitted.

I want to show you what this form request looks like. On the left you see the information request for plasma blood centers and on the right information for blood centers. I'm showing you this now so you can see the actual forms. Don't worry about trying to read all the details because on the next slide I'm going to walk you through exactly what we're requesting in this form and what information you need to provide.

All right. Let's walk through it real quick. What are we requesting?

We request a summary of major deficient nations. Just show us how your quality system functions whether you're identifying problems, investigating them, and implementing effective corrective actions. We also request information on donor adverse events because donor safety is critical. If you're calling 911 every day or every other day, that's definitely an issue. We request information on donors with reactive test results or require screening tests, including screening and confirmatory test results, and donor notification records. So we need complete donor files for specific numbers of reactive donors, showing the test results, dates received, referral day, notification records, and disposition of the unit collected.

We also request post donation information, showing how you handle situations, where the information received after donation affects the suitability of the product including the reason for deferral, the unit disposition, and the donor status. For Source Plasma centers only we request the initial and periodic qualification of donors, include noting files showing SP testing results. The testing dates and the physician review dates. This demonstrates proper donor qualification and medical review. For blood centers only, we request a summary of the BPBRs, showing what you have reported to the FDA and how you have addressed your deviations.

We ask this only for blood centers because blood centers can distribute products within the state, intrastate commerce during the operational period before full licensure. However, Source Plasma centers cannot distribute any products until the BLA is approved.

All right. I know this is a lot of information. But we are just trying to get to know how your facility actually operates. Now beyond these records that I just discussed that assess your performance, we also ask additional facility information and documents. This information will help us understand your operational set up.

And I'm going to go real quickly to this additional documents. We talked we would request your operational details, when did you open, your hours of operation, how many employees do you have and how many employees are in training, your facility and personnel documentation so we can see who is in charge, your floor plan, to see how your facility looks like, and your staff description, what everyone actually does.

We need information about your management and medical personnel, who is running your facility, who is providing medical oversight. For medical personnel, they must be licensed in the jurisdiction where the facility is located. For Source Plasma we ask for goings substitutes,ed medical profession, whether they are RNs, LPNs, LVNs and we look at the expiration date of the license and the CPR certification. We need all donor screening materials and documents, showing how you educate donors. So here we list a donor history questionnaire, whether you're using the ABB to PPTA, all the donor educational materials, high risk and travel posters, medication list, consent and notice of your donor notification letters.

We need information about your equipment and your computer system. We want to know, the donor script you're using, what equipment you're using for collection, and where do you store the products, and this should also include the validation. Your equipment operator's manuals is

applicable. And you also include information about your computer system, your blood establishment computer software system; whether you're performing ad Marching CASI on site, remote or both. We want to know the programs and functions and 510K clearance number.

Regarding your product information, products that you collect, what is intended use, number of donations listed, number of donors, total number of unit collected. This gift us an idea of your operational volume and activity. Your practice facility, who is performing your testing, who is storing your product, biohazard waste disposal. Who is performing that function, and who is transporting your products.

For Source Plasma centers, we need to know your storage capacity and temperature. Your core freezing temperature, the validation of the freezer. The temperature monitoring system in use, frequency of alarm activations. Is it weekly, monthly, yearly? Number of temperature excursions if you have any, and your contingent plan if the power goes out.

This is a lot. But here's the good news. If you're actually operational, you already have all this information. So just gather the information, organize it nicely, and send it to us.

So let's talk about timeline. No, sorry. Let's make it real simple. Here's your dos and don'ts for your BLA submission. Please do complete all required forms. Submit relevant documents only. And contact CBER before submission. Review for completeness before submission, make sure everything is included.

Please don't submit incomplete forms. Don't submit everything hoping it's right. Quality over quantity. Don't assume all documents apply. And we encourage you not to skip the pre-submission contact.

So follow the dos. Avoid the don'ts and you will be fine. Now, let's talk about timelines.

This is everyone's favorite question, how long is this going to take? The review timeline begins when CBER receives your application. Here's something important you need to know, blood establishment don't pay user fees. What does that mean? They are not statutory requirements for review timelines. There are no legal deadlines we have to meet. But, and this is good news--CBER's practice is to follow PDUFA guidelines for nonuser fee applications anyway.

So for example, an original BLA has a 12 month review clock. Please know that we do anything to complete our reviews sooner, when possible. But this is going to be based on availability of resources and most importantly the completeness of your submission. okay?

So to avoid delays, please submit complete BLAs, respond promptly to information requests, be ready for inspection, don't submit amendments late in the review. This is going to delay the process.

So this brings us to the end of this presentation. Let's summarize real quick what we covered today. We talked about when to submit a BLA, the difference between original BLA and a BLA supplement. We do encourage you to contact us before submitting. And we also talked about what to submit. Your forms, your cover letter, your SOPs, donor materials, facility information.

We talked about the submission process, how you can submit, what happens after you submit what does filing mean? We also talked about the RTF, what does that mean? What do you have to do? And we talked about review timelines for original BLA. So please remember to complete forms accurately. Submit only relevant documents. Contact CBER with questions. Don't submit incomplete information. And don't assume more is better.

I've been telling you to license to our presentation to contact us. So let me make sure you know exactly how to do that. Here's your contact information. If you would like to discuss your plans before submitting a supplement, we recommend requesting a meeting to review your approach and any questions you have.

Cherry Geronimo can help you schedule a meeting with OBRR to discuss your plans. And we have included her email here on the slides. For questions related to a supplement that's already on the review, please contact your regulatory health project management, that is listed in your acknowledgment letter. If you have general inquiries that do not require a meeting and you need clarification, please email us at the CBER OBRR inquiries mailbox.

I know this was a lot of information. But I am confident that we will no longer be refusing to file your supplements. You why? Because now you know everything you need to submit, how to submit a complete, well organized BLA the first time. So there's really no excuse anymore. We hope to see you on the happy path, the one that leads to approval and not RTF. So thank you so much for attending this webinar. Now, I am going to turn this over to my colleague, Camilla Smith who will be discussing the BLA review process.

>> CAMILLA SMITH: Good afternoon. Greetings to our global audience. Thank you for joining us this afternoon. I'm Camilla Smith, I'm the lead consumer safety over for the blood and plasma branch. Blood and plasma branch consists of 13 dedicated Consumer Safety Officers.

These officers are reviewing your product submissions, and they're traveling to your very first product inspection. We want you to be successful in your review process. So let's begin our discussion of the biologics license application review process.

Our learning objective during this session is to explain the BLA review process and common deficiencies in your suspicions. Con deficiencies will be discussed here and during the Q&A session at the end of today's agenda.

The goal for CBER is to develop a BLA review process that is efficient and effective for all new license applications such as your original BLA and for established license firms such as your supplements which are considered BLS.

The manufacturer is the applicant. The applicant is expected to create an application that is likely to satisfy regulatory requirements and should be well written so that the Consumer Safety Officer can readily review your submission. FDA will review each document included in your application to determine if it meets regulatory requirements for approval of the manufacturing process for the biological product.

FDA will then send the applicant questions for clarification during the review. It is essential that the applicant have active involvement during the review process. The time required to complete review depends on the quality of the submission received.

A successful BLA demonstrates evidence of compliance. Documents to help you comply in this regard includes the current Code of Federal Regulation the cover of this booklet reads title 21, parts 600 through 799. Guidance documents found on the FDA website listed here, your operator's manuals for your devices, your regulations can be found in title 21 part 606.65e. And your package inserts for reagents as well as your supplies found in title 21, part 606.65e.

Let's discuss a sample of potential delays in completing your review. Avoid submission of SOPs or documents that are not required which means they are not relevant to the manufacturing process or the manufacturing change. Always include a cover letter. Submit all documents that are referenced in your SOPs. If your SOP references a job aid or a form, submit this job ate or form. If you have an SOP that reference a key or a legend, please submit this job ate key or a legend. Make sure that your SOPs are consistent with the package insert, the operator's manual, and your current code of federal regulations.

If your SOP is missing steps that are listed in the package insert or the operator's manual, that will likely cause a delay in your review because an information request will be needed to be created.

Next, and this is essential. Title 21 part 606.160 speaks of records regulations, implementing a blood establishment, computer software system is essential to help you comply with the records regulations.

Key BLA review steps include the following:

The CSO will perform a comprehensive review and document their findings. And an information request will be sent to the applicant to obtain clarification. The CSO will present findings and preliminary regulatory recommendations during this mid-cycle.

An inspection will be conducted if applicable. A review memo is finalized as well as a request for a compliance check. And then a letter to the applicant with the regulatory decision is created.

Whether a BLA or BLS, it will likely include the following listed documents. And these are the materials that we will review in your submission. The cover letter and the table of contents. The table of contents is important to make sure that the content of your submission matches all of the documents that we receive.

A form FDA 356h, the FDA 2830 registration form, and if applicable, your container labels and your extension of labeling which is your circular of information. Chemistry and manufacturing controls which includes your SOPs, validation summary and data, quality control and other applicable documents such as your PI and your OM.

Additional material reviewed include your cover letter. Your cover letter should be signed by an authorized official which is a person designated by the applicant to communicate with the FDA on behalf of the applicant.

Identify the facility in which you are requesting approval by listing the registration number and/or your license number. Clearly state your request. And reference all previously approved SOPs, and comparability protocols if applicable.

Here are some common mistakes that we find in cover letters. A cover letter is not signed by an authorized official. Your cover letter does not have a current date. The registration number of the facility where the manufacturing processes occur is not identified in the cover letter. And your cover letter is describing an obsolete process. So the manufacturing process that you are asking for in your cover letter, you are not actually currently manufacturing at your facility.

Labeling terms which we review. Your container labels and your circular of information, these regulations can be found in title 21 CFR part 606.121 and section 122. For blood collection establishments, please submit copies so that we can review these copies of each of your container labels. So after your submission, we will review the tables. Now, for blood establishments, this should be a full face container label, including all four quadrants. License firms should display their license number on your label for review.

And please make sure to submit your facility specific pages within your circular of information.

Regarding your standard operating procedures, we will review them and the regulations that will help you is within title 21, part 606.100. Make sure, as you are revising your SOPs in regard to our information request, make sure that you submit to us those revised SOPs. Your SOPs should show approval by your responsible physician, your equipment maintenance and calculation schedules and procedures to also be included.

regulations under title 21 part 606.170a, talked about complaints for your adverse reactions arising as a result of blood collections that are, should be investigated and documented. Remember that your personnel who are responsible for the collection, the processing, the compatibility testing, the storage or distribution of your products should be adequate, adequate in number, in educational background, in training, and experience. this is important in the creation of your SOPs.

All right. It will also be evaluated in your upcoming inspection.

This slide demonstrates some common mistakes that we find in your SOPs. SOPs have major changes that are submitted in an annual report. SOPs are submitted to FDA without a new version number or evidence that it was approved by your responsible physician.

Acronyms are included in your SOPs, and they are not defined. Failure investigation steps are missing. The role of the quality assurance unit is not addressed. Your SOPs are not consistent with the device manufacturer's instructions or operator's manual. And SOPs are not relevant to the manufacturing process change in the supplement.

Validation and quality control data review. For this aspect of your review, we would like to point out that the FDA has recommended guidance documents to assist you. For example, here

is a guidance document that was published September, 2012, entitled prestorage leukocyte reduction of whole blood and blood components intended for transfusion.

So please take advantage of the guidance documents listed on the FDA website for assistance in this area.

Additional documents that we review within your submission may include the donation type, volunteer or paid donations; your BECS, as we stated; your collection devices will be reviewed. Your physician substitute program, if you are a Source Plasma facility, please include your physician substitute program within your submission. Position descriptions, medical oversight, your registration form, your QA unit and corporate duties; list your contract services. And list your equipment. Include your donor informed consent, SOPs, and the operator's manuals.

Let's talk about a comparability protocol. What is the comparability protocol? A comparability protocol is submitted initially as a prior approval supplement. And it may be combined with a product manufacturing supplement.

This describes tests and validation studies and the acceptable limits to achieve and demonstrate a lack of adverse effects. Once approved, a comparability protocol allows for a lower reporting category for the same change, using the same device, implemented in an affiliated center. For example, your PAS in the future can be downgraded to a CBE-30.

Let's examine a scenario in which the applicant does not use a comparability protocol.

The applicant requests implementation for the manufacture of aphreresis platelets at seven centers using instrument X. Center 1 develops SOPs, performs testing, validation, and training. Center 1 then submits a PAS.

The FDA reviews and approved the implementation that center 1 has submitted. And this means that center 1 may begin interstate distribution of the licensed product. However, to implement change at remaining centers 2 through 7, the applicant must submit a PAS each time. Let's examine the same scenario when the applicant uses a comparability protocol.

In the same example, the applicant could develop a comparability protocol with its SOPs and form testing, validation, training and submit the comparability protocol with the PAS for center 1.

FDA will then review and perhaps approve the comparability protocol and implementation of the change at center 1.

This means that with a comparability protocol that is approved, the future implementation of the comparability protocol may be reported as a CBE30, provided it follows the plan devised in the comparability protocol.

A CBE30 is only applicable if it the additional facility has an inspectional history.

This slide demonstrates the documents that we review for comparability protocol. The FDA form 356h, your cover letter, your cover letter should request a CBE30 downgrade for supplement, subsequent implementation at affiliated facilities; your SOPs, your records, your

forms, your QC logs, your labeling information, the description of your change, the implementation plan and the training. Tests and validation protocols, product acceptance criteria, quality assurance oversight, your validation summary and two months of consecutive QC, your QC testing procedures, your sampling plan, and your actions for failed results.

At this point, you've submitted your BLA or your BLS. And you've identified whether you would like to have a comparability protocol. Are you now inspection ready? When an inspection is required, all inspection related information is included in your review file. After the inspection, if a 483 is issued, written responses to all 483 items should be submitted to CBER. And inspection findings are documented in reviewed for inspection classification. Remember that inspection findings are considered when making final regulatory decisions.

My colleague Catherine McGraw will present more on the topic of inspections following this presentation.

Possible outcomes. Remember, if your facility which is examined through an inspection and your manufacturing process for the product meet the regulations. Here are your possible outcomes.

Approval: Approval means that your establishment and your manufacturing process for the product meet the applicable regulatory requirements.

A complete response letter-- a complete response letter occurs when a single cycle, a single review cycle approval is not achievable. CBER may issue a complete response letter in this instance. The deficiencies are identified in your complete response letter. And in the unsatisfactory or unresolved inspection findings are also listed.

When it comes to approval letters, for an original BLA, this describes your product which you manufacture, the name of your facility, your license number, and your applicable labeling. For your BLA supplements, this approval letter will describe your manufacturing change and product, the name of your facility or facilities, and your applicable labeling.

When we describe the complete response letter, understand that the complete response letter lists all deficiencies identified. And it recommends actions necessary to address the deficiencies. A complete response letter stops your review clock. And this means that the applicant must submit a response within one year or withdraw the application. The review clock restarts only when the responses satisfactorily address all issues in the complete response letter.

If a response is not received from the applicant within one year, FDA may consider such a failure to respond as a request to withdraw the application or the supplement. FDA will notify the applicant in writing. And the applicant will have 30 days to respond. If the applicant fails to respond, the application or the supplement will be deemed to be withdrawn. And FDA will send a withdrawal letter.

Please remember that part of the review process is a compliance check. What is a compliance check? A review of each manufacturing location included in the BLA or the BLS supplement. This is a compliance check. This means that for each location that's affected by the

manufacturing change, a review is performed to ensure that there are no ongoing or pending investigations or compliance actions.

This applies to both BLAs and supplements except for minor labeling changes. And this must be completed, this compliance check must be completed before issuance of a license or approval of as a supplement.

Continuing on with the compliance check, please note that OBRR will request a compliance check after determining that the application can be approved. FDA inspections must be completed and closed before the compliance status can be determined. OCBQ, the Office of Compliance and Biologics Quality, they perform the compliance check. OCBQ may not recommend approval of a submission when the compliance status is unacceptable.

So this is essentially why we perform inspections. If you have not been inspected, this means you do not have an inspection history. And if you do not an inspection history, you cannot pass the compliance check. A warning letter, an official action letter will deem an unacceptable compliance check. If you would like to license aphreresis red blood cells but you do not have an inspection history at that registration number, an inspection of that location, that facility manufacturing the products is needed for this inspection. So you have submitted a product for licensure. But the registration number, location does not have an inspection history. An inspection will be add today your product submission. And remember, you may not distribute that product out-of-state unless the product is licensed.

If the compliance check is acceptable, your regulatory health project manager will draft an approval letter. If the compliance check is unacceptable, the approval process stops, a CR letter is sent to the applicant, and the review clock is stopped.

Here is a slide based on our timelines. And these timelines are voluntarily. This is a risk based slide, beginning with the prior approval supplement. Remember your prior approval supplement is a list of major changes in our timeline, our voluntary timeline is between 9 and 12 months. Our CBE30 and CBE supplements are a list of moderate changes and are voluntary timeline is 6 months. The annual report, a list of minor changes is a six month timeline. And our special labeling supplement falls into the category of CBE. This timeline is five months.

Okay. So now we've completed our BLA review. You've had your inspection, if necessary. And perhaps you've also submitted a comparability protocol.

Congratulations. You're now licensed. Now what are your next steps? You are responsible for the safety of your products. We expect that you can place your license number on your container labels. Having a licensed product means you can distribute this licensed product interstate which is a different state if you choose. Approval letters are specific to the address of your manufacturing site, the product which is licensed, and the method and the product characteristics.

Your reporting official shall maintain your registration form with the FDA. Maintain your current and correct registration and product listing information, be prepared to explain any discrepancies on your registration form. During inspections your registration is reviewed and we

expect that it is accurate. And during the year, make sure you notify CBER of any moderate and major changes to the approved license including contractor changes.

Be prepared for FDA inspections, and make sure that you understand the regulations. Submit an annual report each year, listing your minor changes.

Let's summarize our key takeaways:

It is essential to submit all relevant documents for review. This allows for comprehensive and timely review.

Review process is interactive. And the FDA may request additional information or clarification.

OBRR will perform inspections if applicable.

A compliance check is required before approval of an application.

Regulatory decisions may be approval or a complete response.

Licensed establishments should be aware of their responsibilities after approval.

Thank you for your attention. And I'm pleased to present our next speaker, Cathy McGraw who will talk to you about the inspection process.

>> CATHY MCGRAW: Okay. Hello, everyone and welcome to today's webinar. My name is Cathy McGraw. And I'm a Consumer Safety Officer at the Office of Blood Research and Review at CBER. Today, I will be focusing specifically on the pre-license and pre-approval inspection process, what it involves, what to expect, and where we most commonly see deficiencies. I hope that by the end of this session, you will leave with a clear picture of how to prepare and successfully navigate an inspection.

The objective for this session is to describe the pre-license and pre-approval inspection process and common citations. We will spend a significant portion of our time on pre-license and pre-approval inspection process itself and the most common citations we issue.

So let's start with the basics. What exactly is an FDA inspection? According to the investigations operations manual section 1.1, 5.1.2 an establishment inspection is defined as a careful, critical, official examination of a facility to determine its compliance with the laws and regulations administered by FDA.

There are two types of inspections relevant to this audience. The pre-license inspection or PLI is conducted before a biologics license application is approved. An example would be your brand new establishment with no U.S. license number, and you are requesting a new biologics license. The pre-approval inspection, or PAI is is specifically for current biologics facilities prior to approval. An example of this would be, if already have an existing license for your establishment, and you want to add a new facility under your current license, and you want to manufacture other blood components such as platelet aphreresis at the new facility. Those share the same core purpose. And this is to verify data integrity, ensure compliance with current food manufacturing practices, and confirm that the facility is truly ready to manufacture the product

it's seeking approval for. A surveillance inspection is another type of inspection. And this is conducted as a routine assignment with no other indicators of noncompliance.

These are your subsequent inspections, and these are conducted by the Office of Inspections and Investigations.

So what gives FDA the authority to conduct these inspections? The primary, legal authority comes from section 351, A1 of the Public Health Service Act in 42 USC 262. And this requires FDA to determine that the biological product is safe, pure, and potent, and that the facility meets the standards to ensure it remains so before approval is given.

Adding to the PHS Act 21 CFR 601.20d makes it explicit that a biologics license shall only be issued after an inspection of a listed establishment and a determination that it complies with the standards in the BLA and applicable regulations. So the inspection isn't just a formality. It is a legal prerequisite for licensure.

Pre-approval inspections are typically generated by a prior approval supplement or also known as a PAS submission. These are required for major changes. A major change is defined as one that has substantial potential to adversely affect the identity, strength, quality, purity or potency of the product. In other words, changes that could meaningfully impact product safety or effectiveness. The approval decision is also based on an acceptable compliance check which draws on the facility's prior inspection history. Your inspection history matters and is part of an ongoing compliance picture FDA maintains for your facility.

So let me give you some examples of situations that will require a PLI or PAI. Opening a new blood collection facility or a new Source Plasma facility will always require an inspection before licensure. Initiating a new program such as an RBC immunization program, adding a new collection site with a specific manufacturing process to a facility that does not yet have an inspectional history at that site also requires an inspection. For example, this would include a facility collecting platelet aphreresis in aphreresis red blood cell products that currently has no history of inspection and seeks licensure for those particular products.

BLA supplements based on new technologies or complex changes that could impact the product will typically require a PAI as well. If you are ever uncertain whether a change or a new activity at your facility would generate an inspection requirement, I encourage you to reach out to OBRR proactively. It is always better to ask in advance than to proceed and find out later that an inspection was required.

Once an inspection is scheduled, the facility, the facility's authorized official will be notified by email approximately 30 days in advance. That notification will include the inspection dates and times, the location, the name or names of the inspector or inspectors who will be conducting your inspection. There is an important requirement here taken from 21 CFR 600.21, the establishment must have been in operation for a sufficient timeframe to demonstrate its ability to manufacture the product or complete the process for which licensure or approval is being sought.

As Miriam stated in her presentation earlier, a minimum of three months of data is needed to conduct these inspections for Source Plasma and six months for blood centers.

When you receive that notification, there are a few things that we ask of your facility. First, please provide the names and phone numbers of key staff who can serves as emergency contacts during your inspection time.

Second, share any special logistical instructions. These would include parking information, parking fees, and any area construction that might affect our ability to access the site or cause delays to your facility. And lastly, make sure that blood collections and any processes pending licensure are scheduled to occur during the inspection period. We need to observe these operations firsthand.

Preparation is one of the most important things a facility can do. We have a few recommendations to help you prepare. Start by reviewing your application data and ensure it aligns with your operations. Discrepancies between what you submitted to the FDA and what you're actually doing on the floor can be a red flag. Conduct internal audits and mock inspections with your staff. Do not wait for the FDA to find problems you could have identified and corrected yourself.

Prepare your documentation in advance. And these include records, validation reports, quality control records, and SOPs. And these should be organized, current, and readily accessible. Ensure that key personnel will be available during this inspection. We need to speak with the people who perform the work, not just your management team. And designated a conference room or dedicated space for the inspection team to use throughout the visit.

On the day of inspection, the process begins when FDA presents their credentials in a form FDA 482 which is the official notice of inspection. This is the official start of your inspection.

The opening meeting will typically include introductions, a discussion of the inspection scope and schedule; a review of your organizational structure, and a tour of your facility.

During the inspection, we will be reviewing a wide range of documentation and records. And you probably ask why. So I will tell you this includes standard operating procedures or your SOPs. This is to verify that written procedures are current, approved, and reflect practices and that staff are following your established SOPs.

Your informed consent, donor acknowledgment, aphreresis consent, this is to ensure donors are fully informed of your procedure and its associated risk prior to giving consented. And then all consent documentation is complete, properly signed and obtained beforehand.

Your deviations as well as your CAPA records, we assess whether the facility is effectively identifying, investigating, and resolving procedural departures in whether corrective actions are addressing root causes and preventing recurrence.

We also confirm that the facility has a functioning process for receiving and acting on information disclosed by donors after their donation for post donation information. For donor adverse events, we assess whether follow-up and action were taken for donor adverse events at your facility. This includes 911 transports in moderate to severe reactions. And to verify that all

reactions occurring or after a donation are properly documented, managed and followed up on. Essentially we identify any trends that may indicate a need for process improvement.

Donor deferrals, we confirm that eligibility criteria are being applied correctly and consistently. And that deferred donors are properly notified with accurate records that you've maintained.

We also will be looking at equipment and process validation. Validation of equipment processes, we confirm that all critical equipment and processes have been formally validated before being placed into routine use, ensuring they consistently perform as intended.

Adequate equipment qualification, this includes your installation qualification operational qualification and perform qualification also known as your IQ, OQ, and PQ. Your IQ would involve installation and configuration of the equipment. Your OQ does your equipment operate correctly? And your PQ, does the equipment perform as intended consistently?

We will also review quality control and maintenance records. This is to confirm that QC testing is performed at required intervals with results within acceptable limits. And that preventive maintenance is conducted on schedule to ensure equipment remains in proper, working condition, preventing failures that could impact product quality safety and integrity.

Serum protein electrophoresis, these are also known as SPE results. We confirm that donor SPE results are being reviewed and interpreted by qualified personnel with appropriate actions taken and that donors with abnormal results are being restated by your responsible physician and handled accordingly at the center.

Additional areas of review will include relevant transfusion trans knitted infection also known as RTTIs. And we assess donor deferral compliance, product dispositioning quarantine, lookback process, donor notification and counseling. And we verify that donors with a normal reactive test results are timely and appropriately notified in accordance with regulatory requirements. That counseling is conducted by qualified personnel and that all related activities are properly documented.

We also review your temperature records as well as temperature excursions that occurred at your site. We verify the products are stored within required temperature ranges with continuous and accurate monitoring, and that any temperature excursions are identified, investigates, and that affected products are appropriately handled. We also look at CPR certification of your staff to verify that the certifications are current, properly documented, and renewed at the required intervals.

Your responsible physician and physician substitute licensure, we confirm that your licensure records for your responsible physician and any physician substitutes are current and appropriate for the jurisdiction in which the collection establishment is located. We also will inspect and copy as needed any required records. This is to exercise the authority to review and obtain copies of records necessary to assess the facility's compliance and applicable laws and regulations and to ensure that all findings are thoroughly documented and supported by evidence gathered during the inspection.

We will also make appropriate recommendations of actions needed. And this is to ensure that any identified deficiencies are translated into clear recommendations for regulatory action and that compliance gaps are addressed through appropriate and timely follow-up actions to protect the public health.

It is important to note that this is not an all inclusive list and reasons we review these records. The scope of an inspection can vary depending on the facility, the type of licensure being sought, and officials made during the visit. The best approach is to make sure the records are always maintained at your facilities.

Beyond document review, we conduct eyes on visual observations of your actual operations. We are watching how things are done, not just how your SOP says that they should be done. So what are some of the things that we are observing at your facility?

Since the start registration will be the first, we verify that donor identity is properly confirmed before donation use an appropriate identification. Verifying the donor's address and all required donor information is accurately collected.

For donor screening, we are looking at that staff following established SOPs, using current and approved screening tools correctly, appropriately identifying and responding to any red flags that are raised during screening process and accurately conducting and recording all required donor measurements and assessments.

Physical exams, we confirm that physical exams are performed by qualified personnel in accordance with regulatory requirements and SOPs, and that any abnormal findings that are appropriately evaluated and addressed before the donor proceeds.

Donor eligibility. To verify that eligibility determinations are made correctly, consistently and by qualified personnel, supported by complete screening and physical exam data and that ineligible donors are appropriately deferred and that the basis for the deferral is clearly documented.

Donor privacy. We are looking to make sure that there is adequate, physical safeguards in place to protect donor's confidentiality, that sensitive conversations are conducted privately and that donor records and personal information were handled and stored in compliance with applicable regulations.

Donor collections. We verify that staff are following proper aseptic technique and SOPs during the collection process. That donors are appropriately monitored for any adverse events or concerns that may arise. And that equipment used, collected volumes and collection data are all within required standards.

Labeling. We verify that product labeling is accurate, complete, and applied correctly in accordance with your established SOPs and controls.

Processing. We verify that your processing steps are being followed and products are placed in the freezer in accordance with the established procedures and SOPs.

And finally storage. To verify that products and supplies are stored under the correct temperature specifications and temperature monitoring and alarms are working and in effect.

At the end of each day, each inspection day, the inspector will do an end of day meeting. This will entail a daily summary to recap what was reviewed or observed that day. The inspector may also discuss any observations, findings or any deficiencies or areas of concern. Inspector will also go over any outstanding items or things that need followed up. This is anything that was not resolved and requires action the next day. Lastly we may discuss the next steps and schedule for the next day. And this will ensure that everyone is aligned and prepared.

At the end of the inspection, we will hold a closeout meeting. During this meeting we may discuss what we call none reportable observations. This include minor regulatory deviations where the potential impact on product quality or safety is not significant enough to warrant a 483 observation. These are also known as discussion items. Deviations from FDA guidance documents may also be raised at this meeting. And remember that guidance documents represent FDA's recommendations not binding requirements but deviations are still worth discussing and understanding.

The closeout meeting may also include discussion of future follow-up items. Issues that are identified during the inspection that will be monitored or revisited at the next inspection. This is also an opportunity for open dialogue between the inspector and the facility. Facilities can clarify their practices, provide context and ask questions. We can explain the basis for your concerns.

I encourage facilities to engage constructively in this conversation. Inspection process is not adversarial. FDA's goal is the same as yours, ensuring that safe, high quality products reach the people who need them.

If anything objectionable conditions are observed, we will issue what's called a form FDA 483 to the most senior official on site at the time of the inspection. The 483 notifies the facility of conditions that, in the inspector's professional judgment, could result in the release of unsafe products. It's important to take this seriously. Facilities should provide a written response addressing each observation within 15 days.

When responding to a 483, provide your written response within the 15 daytime frame. You will need to address the root cause of each observation and include corrective and preventive actions with realistic timelines. For example, if a staff member failed to follow an SOP, you need to ask why was the SOP unclear? Was training inadequate? Was there a staffing issue? Demonstrate that management is committed to resolution where possible, provide evidence that corrective actions have already been implemented.

Be specific. Vague commitments like we will retrain staff without further details are not sufficient.

Once the on site inspection is complete, the process continues. If the facility received a 483, the facility should respond to those deficiencies after the inspection. The inspector prepares an

establishment inspection report also known as an EIR which serves as a comprehensive and detailed account of the inspection findings and review.

An endorsement is another step in the process. This can conducted by our sister office, the Office of Compliance and biologics quality also known as OCBQ. This is where we have reviewed your establishment's inspectional observations and determined that there are no significant violations and that all issues have been resolved to the satisfaction of the agency.

A compliance check will also be performed. And this is based on the outcome of the inspection that we just conducted. This is to verify and ensure that your facility is operating in accordance with the regulations. If everything is satisfactory, the inspection findings are acceptable, the facility's responses are adequate and compliance checks are clear -- congratulations. An approval letter is on the way.

There are three possible inspection classifications. The first one is no action indicated or also known as NAI. This means that the facility is in an acceptable state of compliance. This is the best possible outcome. And this is what you want.

Voluntary action indicated or VAI means that objectionable conditions or practices were found. But the agency has determined that the facility can voluntarily correct its deficiencies and will not recommend any action.

Official action indicated, or OAI means a facility is in an unacceptable state of compliance, and formal regulatory action may follow. This is not what you want.

The inspection outcome directly affects your BLA. A complete response letter or CR means the application will not be approved until identified deficiencies are resolved. In some cases, approval may be with held pending reinspection. If deficiencies are minor and have been adequately addressed the in silt's response,ed application may proceed to approval. The path forward depends heavily on the nature of the findings and your responses.

Now, let's look at some data. This slide summarizes the 483 citations we've issued between 2022 and 2025. As you can see, the rate normalized for the number of inspections performed each year. Even though inspections are announced and facilities know when we are coming, we continue to find deviations from regulations despite the relatively low number of 483 citations we issue. For every 483 issued, many more observations and discussion items are identified during the inspection. Giving facilities the opportunity to make corrections before receiving their license and before surveillance inspections begin, it is important to note that surveillance inspections are conducted again by the Office of Inspection and Investigation which this is not our office.

I am now going to walk you through some real-world examples of 483 citations. These are drawn from actual inspections and represent the type of issues we encounter most frequently.

As we review these, I'd encourage you to think about whether similar vulnerabilities might exist if your own facility's operations.

Let's talk about lookback. This citation involves a failure to conduct timely lookback. The regulation requires that consignees be notified within three days of discovering a donor who tested reactive for anti-HIV 1 and 2 and confirmed positive. In this case, the facility's SOP didn't address the appropriate steps when units collected at multiple centers were involved or which location or corporate entity is responsible for notifying consignees. This is a critical gap. Lookback procedures must be comprehensive and clearly assigned responsibility especially with multisite operations.

Next, we have RTTI testing donor notification, and counseling. This citation was issued because the facility failed to further test each donation, found to be reactive by a donor screening test, as required under 21 CFR 610.40e. This is not optional. But this is a regulatory requirement.

Here is another RTTI donor notification and counseling. This citation under 21 CFR 630.40b involves a Source Plasma facility that failed to include all required information in its donor notification and counseling messages, specifically the notification letter did not clearly state that the donor was deferred ineligible to donate again. And the facility did not consistently include all additional test results in the notification. Donors have a right to complete and accurate information about their test results and deferral status.

Here's another RTTI testing. Donor notification and counseling. This falls under 21 CFR 630.40b as well. This time, it's focused on donors who did not return to the collection center after being asked to do so. The facility failed to provide these donors with the required information, the reason for their deferral, the types of donations they should no longer make, their test results including any additional testing and information about medical follow-up and counseling.

The regulation does not allow facilities to simply stop at the notification process because a donor does not come back.

Next we have responsible physician. These citations were due to staff other than responsible physician who were not physicians, reinstating deferred donors for abnormal SPE and total protein results. Basically in both of these cases, reinstatement was not being performed by the responsible physician. The regulation is very clear. A responsible physician, one who is licensed to practice medicine in the jurisdiction where the collection establishment is located, must be involved in these reinstatement decisions and processes.

Current good manufacturing practice or cGMPs. This citation covers two related issues. First the facility failed to recalibrate a weight used for daily QC checks on a cell separator according to the required schedule.

Second, the facility had been using freezers to initially freeze and store Source Plasma without ever completing a performance qualification. You must demonstrate that your equipment performs as designed of before relying on it for product freezing and storage.

These citations under 21 CFR 6036.100b reflect a recurring theme. Facilities not following their SOPs. In one case, reagents and supplies were not stored at manufacturer recommended temperatures. In another, the staff failed to make copies of donor notification letters as required

by their own SOP. Making it impossible to determine from the records what information was actually provided to the donors. Your SOPs are your commitment to compliance.

If you write it, you must follow it.

This next citation involves a technician who deviated from both the SOP and the operator's manual during QC of refractometer, specifically by covering the instrument with their hand to block am by orient light. A step not outlined in the firm's SOP, the operator's manual specifies that shielding from ambient light should only occur when an error code is displayed.

This is another failure to follow SOP. This citation combines 21 CFR 606.100b and 606.160a1 and addresses two related issues. Staff do not always follow SOPs for manufacturing steps and not documenting results concurrently. Concurrently which means at the time the work is performed. Concurrent documentation is the fundamental data integrity principle. Documenting after the fact introduces the risk of errors, omissions, or in the worst case scenario, falsification of records. Records must reflect what happened and when it happened.

Personnel. This citation falls under 21 CFR 606.20b. The facility lacked an adequate number of permanent employees in critical positions, specifically the center Director, quality assurance supervisor and physician substitutes. During the inspection, these individuals were not present or could not demonstrate competency in their assigned functions.

As we wrap up the essential content, I want to leave you with some key takeaways on operational readiness. Conduct thorough self-assessments regularly. Don't wait for an inspection to find your gaps. Make sure your facility's actual operations align with what is in your application. Train your staff on inspection readiness as an ongoing practice, not a one time event. Maintain strong quality systems year-round. And practice data integrity principles every single day. Compliance is a culture. It's not just a checklist.

There are a number of resources available to help you prepare. And these include the FD&C Act, the PHS Act 351A1, and 21 CFR part 600-680. Your operator's manuals and package inserts for your equipment, compliance program, guidance manuals, compliance policy guides, inspections operations manual and FDA guidance documents. I encourage you to familiarize yourself with these resources and use them proactively.

Here are some key references from today's presentation. These are all publicly available. And I encourage to bookmark these. I want to thank you for your time today. We are now going to take a break. We are not going to take a break. Sorry. I think we went over a little bit.

I am going to introduce Dr. Wendy Paul. Thank you.

>> DR. WENDY PAUL: good afternoon, everyone. And I just want to thank you for your patience and for hanging in there with us. We did go a little bit over time this afternoon. So we are going to skip through the break. We're going to skip the break this afternoon. If you're sitting at your desk or in a room where you can stand up and stretch your legs while we continue to talking, we're going to move onto get to our Q&A session. You can see how passionate our

blood and plasma branch is about getting you the information you need to get a good grade on your homework.

And we want to remind you that these presentations will be available for future reference as well as a recording of the session. But at this time, we're going to skip right to the Q&A session. And I'm going to bring back our branch chief, Miriam Montes. Thank you for your patience.

>> MIRIAM MONTES: All right. I'm back. Let's go ahead and start with the first question. Question number one. For first time BLA applicants, what are the most common deficiencies identified during FDA review? I think we already talked about this. We will refer you to presentations from this morning to answer your questions.

For first time applicants, we recommend that you contact us for information on what is needed in a BLA. Some of the most common deficiencies include missing or inadequate standard operating procedures and documentation as well as insufficient evidence of compliance with the CFR requirements.

We also observed failures to comply with cGMP processes because the establishment the did not implement a broad establishment security software system for donor and product management. Please note that relying solely on manual paper system is problematic because they often lack the necessary controls to prevent errors, to ensure product safety, and maintain records as required in 21 CFR 606.160. Additionally, applicants sometimes fail to provide adequate data, demonstrating the product's efficacy, safety, purity, and potency.

Moving to question number two. What general timelines should applicants expect from original BLA submission through licensure decision?

As for timelines, applicants can expect the acknowledgment to the BLA submission within days of receipt, approximately two weeks.

The FDA typically makes a filing decision with approximately, within approximately 60 days after we receive your application to determine if it the application is complete for a meaningful review.

If an inspection is needed, the applicants receive at least 30 days advanced notice. The entire review process from original BLA submission to finalizing decision, generally takes 12 months. Although these timelines depends on resource availability and mostly depending on the completeness of your application.

Moving onto question number three.

When submitting a BLA supplement that references a prior application, what are FDA's expectations for resubmitting unchanged labeling versus cross-referencing labeling from a previous submission, particularly when adding new aphreresis collection sites and the product label does not change?

For a supplement to a BLA, FDA allows applicants to cross reference the STN under which the container labels were previously approved. That is only provided that the applicant can attest there are no changes to the previously approved container labels.

This means, you do not mean to resubmit on change labeling in your, in its entirety. Instead you may reference the prior STN where the label was approved. However, it's important to know that during an FDA inspection, inspectors may request the review of the actual container label to verify compliance and confirm that it matches the previously approved version.

Therefore, while cross referencing is acceptable for the submission, you should maintain readily available copies of the approved labeling, and be prepared to present them during inspection.

Moving onto question number 4. How should a new establishment with limited operational experience prepare for and demonstrate readiness for an FDA inspection?

And I think my colleague Cathy McGraw just talked about that recently. New establishment should prepare for FDA inspection by ensuring the facility is operational for how long? For a minimum of 3 months with comprehensive operational data before submitting the BLA.

Before inspection, the facility must have manufacturing activity ongoing, personnel fully trained and competent, operations and processes validated and all operations must be compliant with applicable CFR requirements. And the facility register for 21 CFR 607.21. Preparation involves establishing that the facility is fully operational. This includes comprehensive staff training, complete equipment and system validation, and implementation of all required SOPs.

Collecting operational data, your facility metrics, deviations with CAPA, adverse reaction reactive test results and organizing your documentation. Please have your documentation readily available.

Demonstrating readiness during inspection requires showing active operations. Your staff competency, validated equipment, functioning quality systems and complete organized documentation with traceability from topic to product. Key personnel must be available to explain the quality systems, deviation management, and regulatory compliance. The key is demonstrating your procedures are actively used and effective, not just documented.

Moving onto the next question. Please describe FDA's current practices regarding pre-license and pre-approval inspections, including typical inspection notification timelines and the most common inspectional citations observed at new blood collection establishments.

We refer to our presentation on inspection from my colleague Cathy. Pre-license inspections are conducted before approval of a new BLA. While the pre-approval inspections are conducted from major changes with substantial potential to affect the product safety or effectiveness and new facilities under an existing license. The facility's authorized official is notified by email approximately 30 days in advance of the inspection. After the establishment has been in operation long enough, which is a minimum of three months, to demonstrate compliance with regulations. As discussed in the presentations, some of the more common citations are related to the donor notification process, not testing unit collected after a reactive result on the unit,

insufficient personnel and failure to follow SOPs. Other citations were discussed during the presentation.

So now, for the next question, I'm going to have my colleague Camilla Smith go over a few more questions with you.

>> CAMILLA SMITH: Question 6. Can a single submission request approval of both a new facility and licensure of products collected at that facility? Or does FDA prefer these actions to occur separately or in a specific order?

Yes. A single BLA submission simultaneously request both approval of a new facility and licensure of the blood products that will be collected that facility.

Please provide guidance on addressing certificates of inspection during the BLA review.

FDA does not accept certificates of inspection for our BLA review.

For establishments that already hold an approved BLA, may a comparability protocol reference the existing licensed application rather than being included in a new BLA?

Yes. A comparability protocol may reference an existing license application and is submitted as a prior approval supplement under 21 CFR 601.12e.

The comparability protocol establishes specific test, validation studies and acceptable limits to demonstrate that specific types of manufacturing changes do not aversely affect product safety or effectiveness.

Once approved, the comparability protocol allows for reduced reporting category when implementing the specific changes covered by the protocol. However, a comparability protocol is not appropriate for changes requiring pre-approval inspections. Therefore, while a comparability protocol can be useful for certain repetitive manufacturing changes across existing facilities, adding a new collection facility with no inspectional history still requires a standard PAS with approval, pre-approval inspection as this comparability protocol pathway is not applicable for this type of change.

What is the current FDA recommended process for adding a new collection facility to an existing establishment license and licensing products collected at that site?

Adding a new collection facility to an existing establishment license requires a prior approval supplement under 21 CFR 601.12b because this represents a major manufacturing change with substantial potential to affect the product's safety, purity, and potency. The facility must be operational for a minimum of three months with established validated operations before submitting a PAS.

If the new facility has an inspectional history to demonstrate compliance and has been approved with the comparability protocol under 21 CFR 601.12e, a lower reporting category such as a CBE 30 may be appropriate because the use of a protocol mitigates the potential risk associated with the change.

If the new facility has no inspectional history, FDA must conduct an inspection to determine compliance with current good manufacturing requirements. FDA will request facility-specific information from the blood establishment for operational data and will schedule the inspection day.

Why is the addition of a new blood or aphreresis collection center generally considered a major change, requiring a prior approval subpoena belt under 21 CFR 601.12b, when the new site will operate under the same approved policies, procedures, quality system, and organizational oversight as existing licensed facilities?

The addition of a new blood or aphreresis collection center represents a major manufacturing change with substantial potential to affect product safety, purity, and potency. The implementation of manufacturing in a new facility includes validation among other actions.

Therefore, FDA expects submissions to include applicable validation and quality control data. As we noted earlier, blood establishments that already hold an approved BLA may request for an approved comparability protocol. Once approved, the CP allows for IA reduced reporting category when implementing the specific changes covered by the protocol.

However, adding a new collection facility with no inspectional history still requires a standard PAS. FDA relies on the inspectional history of a facility to complete a compliance check. subsequently, FDA cannot approve a submission for a new facility that does not have an inspectional history.

In this case, FDA will conduct an inspection before approval.

Are there any circumstances under which adding a new blood or aphreresis platelet, RBC collection site could be considered a moderate change appropriate for CBE 30 under 21 CFR 601.12c and an inspection would not be performed?

Yes. If the facility has resent inspectional history to demonstrate compliance and has an approved comparability protocol under 21 CFR 601.12e a reduced reporting category such as a CBE 30 may be appropriate because the use of the protocol reduces the potential risk associated with the change.

We understand the requirement to notify CBER of substantial changes in SOPs, terms, testing, or equipment for processing Source Plasma donors.

Could you clarify whether minor changes such as formatting adjustments to internal process documentation or forms used for donor processing, require notifications?

Minor changes that have minimal potential to have an adverse effect on the safety or effectiveness of the product like administrative changes such as reformatting documents or adjusting the layout of forms do not require prior notification to CBER.

Under 21 CFR 601.12, you must report such changes in your annual report. FDA has published specific guidance, published December 2014 entitled, changes to an approved application

biological products, human blood and blood components intended for transfusion or for further manufacture.

This guidance is intended to assist blood establishments in determining the appropriate reporting category. If you are still uncertain of the reporting category, you may contact us for clarification.

The next questions will be answered by Miriam Montes.

>> MIRIAM MONTES: All right. Here I am again.

We're going to question number 13. What are the common raises BLAs are delayed or do not result in approval on first review? When is formal resubmission of a BLA required?

The most common reason that a BLA takes longer to review or does not result in approval is that FDA receives an incomplete submission.

If the submission is incomplete, FDA may issue a refuse to file letter. As outlined in the presentation, RTF stops the review process entirely, requiring resubmission of an entirely new BLA with a new review timeline.

After the RTF, the applicant must submit an entirely new BLA, not as an amendment with all the original content, plus the corrections of all identified deficiencies. A new STN is assigned, and a new review timeline begins.

Once FDA files an application, the CSO will review all documents submitted. If deficiencies are identified and they cannot be adequately resolved through the information request, FDA will issue a complete response letter. Common reasons for an issuance of a complete response letter include manufacturing and quality system deficiencies, donor and product safety concerns, inadequate screening procedures, testing issues, personnel and training deficiencies such as insufficient qualified staff, inadequate training documentation, improperly licensed medical personnel, documentation and compliance issues such as SOPs not followed in practice, inadequate records, regulatory noncompliance, operational performance problems, and inability to demonstrate consistent compliance. After a complete response letter is issued, the applicant must resubmit the application or supplement addressing all deficiencies that were identified in the letter or withdraw the application or supplement.

Next question.

Form 356h is required to be submitted by your blood establishment when applying for a supplement to the BLA. The form contains many fields that are confusing and may not apply to blood and blood products. This questions have three different parts. Part one, can you explain the rationale and applicability of form 356h to blood and blood products?

Form FDA 356h is the standard form used across FDA for all biologics license applications and supplements including those for blood and blood components. While the form was designed to accommodate the full range of biological products regulated by FDA, it serves as a consistent framework for all BLA holders to communicate changes.

The rationale is to maintain a standardized submission format that allows FDA to locate key information. Part two of the question.

Is it possible to create a form specific to blood products?

As stated earlier, the form applies to all biologics products that FDA regulates. FDA does not plan to create specific forms for blood establishment. You may complete sections applicable to your submission.

What are the minimal requirements for blood products that should be included on the form?

Can you clarify which entries on the current form are necessary or applicable specifically for blood products?

Complete only the fields relevant to your submission. At a minimum you should include the applicant information, the supplement type, a clear description of the proposed change, and any applicable manufacturing information.

Fields that don't apply to blood components such as clinical or nonclinical study sections can be marked as NA. The goal is to provide FDA with enough information to understand your change without forcing irrelevant data into inapplicable infields.

Next question. Is there pre-BLA process available for blood centers to address questions and receive feedback in realtime?

Yes, there is. There are mechanisms available for blood establishment to submit questions and receive feedback before submitting a BLA or BLA supplement. For specific questions regarding your future submission, you can request a formal type seat meeting with FDA. You can contact your regulatory health project manager or the regulatory health manager staff chief, Cherry Geronimo. To obtain guidance on how to submit this request, for type C meetings you must submit your questions and relevant background information in advance so FDA can review the materials and provide written responses before the meeting.

This proactive approach allows to you clarify expectations and ensure your submission is complete and compliant.

What is the best way for a blood center to obtain the latest status of their submission?

All questions related to your submission should be directed to the RHPM assigned to your application. Remember, this is listed in your acknowledgment letter. Your RHPM is your primary point of contact and can address specific questions about your submission. If we need additional information from you, the RHPM will proactively communicate this to you.

As we stated in our presentation, while blood and Source Plasma establishments are not subject to user fees, we commit to completing reviews within the timelines established for user fee drug products.

Please describe any best practices for communicating with the RHPM about my submission.

The review process is intended to be interactive as this allows for timely review of application. The CSO reviewing your supplement will request for additional information or clarification by sending communications through the RHPM. When the RHPM requests additional information, we recommend that you provide comprehensive responses and address the underlying questions. If the request is not clear, please ask for clarification before responding.

If your response is inadequate or needs further clarification, you may receive additional questions. The CSO cannot proceed with approval until questions are resolved satisfactorily. Know that, if deficiencies remain in the submission, we may issue a complete response letter and stop the review clock. You can refer to 21 CFR 601.3.

Next question. What is the most effective way for firms to stay up to date on FDA guidance updates, regulation changes, et cetera, that directly impact the Source Plasma industry? Are there specific resources, tools you can recommend?

As you heard in Jennifer Scharpf's presentation, FDA published relevant communications to blood establishment through various channels including the Federal Register notices and via the FDA website. We recommend you check the blood guidances and CBER safety communication websites occasionally.

Also, you may sign up to receive CBER updates via the FDA website. You can scroll to the bottom of any CBER web page and submit your email address to receive notifications of CBER news and new document policy.

Last question. How does FDA respond to complaints from Congress on behalf of the constituents and blood donors, requesting removal from the national donor deferral registry NDDR and reentry as donors? We explained that FDA recommends but does not require blood establishments to perform donor requalification and removal for donor deferral registries. As appropriate, when a donor tests falsely reactive on a screening test for an RTTI, additionally we share the relevant guidance documents that provides requalification method for donor reentry and suggests that the constituents or blood donor contact the blood establishment responsible physician to discuss requalification testing and removal from the Donor Deferral Registry including the National Donor Deferral Registry.

This concludes the questions. Now, I will leave you with Dr. Anne Eder who will be providing the closing remarks for this presentation.

>> DR. ANNE EDER: Okay. Thank you. I'm going to make just some short comments. I hope today was helpful because we all depend on a safe, adequate, and available blood supply.

We don't have the national blood system like the United Kingdom or some other countries. Our system is fragmented. Four of the largest licensed blood centers provide about 50 to 60% of our blood supply. And the remainder of the 71 at about a thousand licensed establishments provide up to probably over 95% of our blood supply with the smaller registere- only, hospital based centers providing the rest.

So we have a very fragmented-- but you can look at this as a glass half empty or glass half full because in every disaster, as I said at the beginning, in every disaster the blood establishments have shown - the licensed blood establishments- have shown that, when blood is needed, it gets moved where it needs to be for our patients. So in cybersecurity attacks, in weather disasters, it gets to where it's needed.

And it's not about opening centers quickly. You heard today-- it can't be done, or it can't be done safely (quickly). We inspect, because we find deficiencies. We review your SOPs because we find deficiencies that you can fix so that you'll pass your surveillance inspections.

So our regulatory framework is flexible. It gives you the flexibilities to continue to collect blood when we're reviewing your SOPs and distribute it within the state as your waiting for your license. So the laws-- or the statutes that we have give us the flexibilities that we need. We have comparability protocols that you heard. We don't need another bill. And sometimes, careful what you wish for.

We talked about what slows down an application. Miriam just answered that question. And we'll be posting the answers. And what she sort of didn't talk about is what I'll just mention briefly. You heard it a couple of times. Blood establishments don't pay user fees. Pharmaceutical companies pay user fees. So FDA when the appropriations lapse otherwise known as the shut down, those reviewers can continue to work on those applications. When appropriations lapse, our blood and plasma branch cannot continue to work on your applications. There are criminal penalties associated with it. So as September, October approaches, if our, if the budget authority, congressional appropriations lapse, hoping they don't-- but that's another cause for delays. Weather as well.

But really, hoping it doesn't happen. It might not. But the elephant in the room as the Fall approaches, will appropriations lapse. And that really is a shut down. Our budget, our Blood and Plasma Branch because we are nonuser fee, we cannot, our Blood and Plasma Branch, all of our staff are furloughed. We cannot work on your applications. And that is certainly a setback for our work on your application.

So just to throw that out there. We know, we understand that your submission is the most important submission. So to you-- we know how important it is to you. So we hope this information has been helpful. We hope that you get on the happy path.

We will be posting these presentations for you. And it is the case that some centers can get licensed more quickly than others. We monitor our turn-around times. And it certainly is-- it certainly is possible to get licensed if your cover letter tells us what to look for. You know, it might be obvious to you. But when you get-- when our reviewers, when our CSOs get hundreds of pages and a cover letter that is lacking, let's say it's a challenge, needless to say.

So I was going to run through, summarizing the high points of our really exceptional speakers. But since we're at time, let me just say that I really appreciate all the work that went into this workshop. We were going to give it last year. But there were-- there was a lot that happened last year. There's stuff happening now as well.

Let me just end with some resources that I think will be very helpful to you. You can contact us. And you heard several times, please do. Please contact us. If you have specific questions about your application, you can contact us. You can come in with a pre-submission.

But please come in through the right pathway. It will help a lot. If you have questions about your regulatory submission, please contact your RHPM. If you want a pre-submission, please contact your RHPM or if it's a pre-submission, contact Cherry Geronimo. She's the chief of our Regulatory Project Management team. We work as a team. And I've never worked with-- our Blood and Plasma Branch, Cherry Geronimo, our Regulatory Project Managers - this is the best team ever, I have to say. I have never worked with a more dedicated, committed, professional team. And they work really hard. And we work as a team. So contact Cherry Geronimo, and she will get the team together. If you have general questions, that is if you're reading one of our guidances, say something isn't clear to you, you can submit a question to our inquiry box.

We get hundreds. We respond to hundreds of questions. So in addition you saw the numbers on our regulatory workload that Miriam and Camilla and our teams manage. We get hundreds. Miriam manages hundreds through the mailbox. Camilla, they answer hundreds of questions through the mailbox.

And that's great. Keep them coming. But you know, please don't send random questions. We're not AI. If you have general questions about CBER, please don't send them to us. Please send them to this address.

And finally, please send us your feedback. We'd like to hear what you thought of today. We'd like to know how we can improve this webinar. How often, if you'd like to hear more specialized topics. There are topics we talked about including, decided not to include. We'd love to hear your feedback. So please send us your feedback. And if you do, send it to this email address. Include OBRR webinar 2026 on the subject line. And we will review all feedback. And if we get questions, we'll review those questions. And we'll add them to the Q&A and post those Q&A on the presentations on the event pages along with our presentations you heard today. I just want to thank our speakers, like I said. This is the best team ever. So thank you. Thanks, everybody. Thank you, blood establishments. As I said, we depend on you for a safe, adequate, and available blood supply and Source Plasma supply for plasma pharmaceuticals. And this concludes our webinar. Thank you.