Ask the FDA and CMS/CLIA
October 10, 2017
AABB 2017 Annual Meeting
San Diego, CA

PANEL MEMBERS
ORIEJI ILLOH, MD, Director, Division of Blood Components and Devices (DBCD), Office of Blood Research and Review (OBRR), Center for Biologics Research and Evaluation (CBER), Food and Drug Administration (FDA)
EMILY STORCH, MD, Medical Officer, DBCD, OBRR
RICHARD MCBRIDE, MS, MT(ASCP)SBB, Chief, Blood and Plasma Branch (BPB), DBCD
JUDY CIARALDI, Consumer Safety Office (CSO), BPB
ANNE EDER, MD, PhD, Associate Deputy Division Director for Medical Issues and Policy Development, Division of Emerging Transfusion Transmissible Diseases (DETTD)
SAFA KARANDISH, BS, MT (ASCP), Consumer Safety Officer (CSO), Division of Human Tissue, Office of Cellular, Tissue and Gene Therapies, CBER
PENNY MEYERS, MA, MT(ASCP)SBB, Technical Director, Centers for Medicare & Medicaid Services (CMS)/Clinical Laboratory Improvement Amendments (CLIA)

MODERATOR
SHARON CARAYIANNIS, Director of Regulatory Affairs at AABB
With assistance on cellular therapy issues from:
KAREN PALMER, Deputy Director of Regulatory Affairs at AABB

MODERATOR: Welcome to our 2017 session of Ask the FDA and CMS/CLIA. We're happy to have you here. I think you'll get a lot of good information. I will start by saying thank you, because our regulators are working on their federal holiday. So, we appreciate that they came to support this session.

I'm Sharon Carayiannis. I am the Director of Regulatory Affairs with AABB. I'll be joined by Karen Palmer later in the program. She'll present the cellular therapy slides, and she's our Deputy Director. We have no financial disclosures. We always have learning objectives, and you can see here that we would like you to know how to apply regulatory strategies for regulations, also for recommendations, and to describe FDA's approach for regulation in various areas. I will say that the folks in ORA at FDA that deal with inspections are very interested in participating next year. So, be thinking of your questions related to inspections throughout the year, and be sure to submit them to us when we send out our request for that.

We'll start with the blood and blood components. Then we'll move to questions on cellular therapy. And then finally, I will be answering questions for the CMS/CLIA activities. Penny Meyer was not able to attend, but she was very gracious in supplying responses to all the questions that were submitted.

I'd like to introduce our panelists.

If you'd just raise your hand. I think a lot of us know who all of you are, but if you would raise your hand as I introduce you. [introductions]

We do appreciate the work that you put in for this session. We'll start with a question about the September 2017 Guidance for requalification of donors previously deferred for a history of viral hepatitis after the 11th birthday.

Background: FDA recently issued this as a guidance titled "Requalification of Donors Previously Deferred for a History of Viral Hepatitis after the 11th Birthday"

Question 1: Please identify the goals of this guidance and key recommendations that provide the path for requalification.

Question 2: Please give examples of donors that would be eligible to donate.

Question 3: Please identify those donors that would not be eligible to donate.

DR. EDER: I'll take this one, to start. The guidance provides recommendations for evaluating donors who were previously deferred for a history of hepatitis after age 11 and allows requalifying donors, if they did not have Hepatitis B or Hepatitis C.

Last year at this forum, we fielded questions about a history of hepatitis and reentry. Because in May 2016, FDA eliminated the longstanding requirement to defer donors with any history of viral hepatitis after their 11th birthday, including types that did not cause chronic post-transfusion hepatitis. The rule also requires, of course, that to be eligible, donors must be in good health and free from transfusion-transmitted diseases. The regulation requires that any requalification method for a health history deferral, such as a history of hepatitis, must be found to be acceptable by the FDA under 21 CFR 630.35(b).

The newly-released guidance does just that. It describes an acceptable process for blood establishments to requalify donors who have been previously deferred for a history of viral hepatitis. It allows blood establishments that choose to reenter donors to develop a procedure to evaluate the reason for the prior deferral and to evaluate their eligibility. If the recommendations in the guidance are implemented without modification, licensed blood centers would simply report the change in their annual report. There are more implementation details in the guidance.

To get to those recommendations, the second question was, "Please give examples of donors that would be eligible to donate." Donors may be eligible for reentry without performing pre-donation testing if the previous reason for deferral was for Hepatitis A, Infectious Mononucleosis, or viral hepatitis due to Epstein Barr virus or Cytomegalovirus. If the deferred donor reports a history of hepatitis but is uncertain about their medical diagnosis, prior test results, or whether they might have had Hepatitis B or Hepatitis C, the responsible physician, to determine their eligibility, should determine if the donor qualifies for reentry. The responsible physician's assessment might include, but is not necessarily limited to re-interviewing the donor, re-reviewing the prior deferral records, interpreting the results of lab tests for Hepatitis B and Hepatitis C, if any are available, and/or referring the donor for further evaluation, as necessary.

The responsible physician cannot delegate this responsibility, but they can make the determination over the phone or by other off-site consultation. I want to just add that, if the center does perform testing for Hepatitis B and Hepatitis C to attain additional information about the donor's infectious status, a sample should be drawn separate from a donation. That's because, of course, donors are not eligible to donate if the purpose is to obtain test results for a relevant TTI, like Hepatitis B or Hepatitis C. So, if the responsible physician determines that a previously deferred donor does not have the evidence of current or past Hepatitis B or Hepatitis C infection, the donor may be eligible for reentry, provided all other eligibility criteria are met.

I've already mentioned or identified donors that are not eligible, that would not be eligible for reentry and would not be able to donate are those individuals who have had Hepatitis B or Hepatitis C infection, regardless of symptoms, spontaneous recovery, or treatment. Such donors must be indefinitely deferred and are not eligible for reentry. FDA has not identified an acceptable method or process for requalification of previously-deferred donors known to have a clinical diagnosis or confirmed laboratory tests for Hepatitis B at any age or a clinical diagnosis or confirmed laboratory tests for Hepatitis C at any age. That's it in a nutshell.

MODERATOR: Thank you for giving the examples of who will not be requalified through this guidance. I know there were some varying interpretations. Thank you for clarifying that.

Iron deficiency risk in donors is a hot topic, and some people are considering vouchers for iron replacement.

Background: Strategies to address the risk of iron deficiency in blood donors have been discussed by FDA's Blood Product Advisory Committee and addressed in AABB's March 2017 Association Bulletin. Blood donor centers are developing approaches to educate the donor about iron loss and iron replacement without treating the donor as a patient. Some blood donor centers are considering providing a voucher for an iron supplement along with donor education materials.

Question 4: Would FDA consider a voucher an acceptable approach?

DR. EDER: Yes, FDA recognizes the effectiveness of iron replacement strategies after blood donation as reported in recent studies and recently discussed at BPAC, especially for targeted subgroups of donors at particular risk of iron deficiency. FDA does not object to the routine use of iron supplementation by providing iron tablets, coupons, or vouchers for iron tablets to reduce the risk of nutritional iron deficiency due to blood donation, that is provided that the iron tablets are meant to replace the approximate amount of iron lost with blood donation using an appropriate regimen of oral iron. So, a short course, low-dose oral iron intended to replace what was lost with the blood donation. Donors should also be counseled about iron loss from blood donation and the benefits and risks of iron supplementation.

MODERATOR: Thank you.

Background: AABB's Donor History Task Force maintains the Medication Deferral List (MDL) for use with the v2.0 AABB Donor History Questionnaire. The package insert for some drugs contains specific language describing the contraindication to donate blood.

- **For example, the package insert for Erivedge states: "Advise patients not to donate blood or blood products while receiving Erivedge and for 24 months after the final dose of Erivedge."**
- **On the other hand, the package insert for Aubagio, a teratogen, states: "Advise patients that Aubagio may stay in the blood for up to 2 years after last dose." But does not contain a contraindication for blood donation.**

Question 5: What resources are available on FDA's website to identify new drugs and changes to the package insert that effect the safety, purity or potency of blood components?

DR. ILLOH: First of all, we don't really have the resources at this time that are available on our web site to identify new drugs that might have blood donor deferral recommendations. Now, we do recognize that this is a longstanding issue that needs to be resolved. We've discussed this with AABB in the past. AABB has brought this to our attention.

I want to truly thank the AABB DHQ Task Force for keeping an eye on all these new medications and updating the medication list, as necessary. Now, like I mentioned, we're aware of this issue. It's a longstanding issue, you know, the new drug approval process and package insert revisions.

FDA is huge. We are CBER. A lot of these things take place in other centers, especially the Center for Drugs. We're still working together to find out the best way to get all this information together. We've not forgotten about this. We're still working with our Center for Drugs, especially, on efforts to develop a process to identify new drugs and changes to the package insert that affect the safety, purity, or potency of blood components. In the absence of resources right now, we appreciate the efforts of the AABB DHQ Task Force looking at this. But if you don't have this on your medication list or you don't use the AABB DHQ material, the expectation is that the responsible physician for that blood center should determine their appropriate donor deferral, based on the information in the package insert of the drug.

MODERATOR: Thank you.

Background: FDA's January 2016 Guidance*, Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products,* Section IV.A.5., recommends that:
You should indefinitely defer former or current U.S. military personnel, civilian military personnel, and their dependents as follows:

- **a. Individuals who resided at U.S. military bases in Northern Europe (Germany, United Kingdom, Belgium, and the Netherlands) for six months or more from 1980 through 1990, or**
- **b. Individuals who resided at U.S. military bases elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for six months or more from 1980 through 1996.**

Question 6: How does this deferral apply to military personnel stationed aboard US military ships docked in-port at these locations?

We get this question with some frequency. So, that's a signal to us that we think people are truly trying to do the right thing. But we also know we never need to defer anybody who does not need to be deferred. That's why this question was included.

DR. EDER: Sure, and I'll take it. Generally, we would not expect that military personnel stationed aboard a ship that temporarily docks at a military base, are not living on the base, and would not spend sufficient time on land to be associated with a risk. So, the cumulative time spent in vCJD countries of risk should be calculated based on the amount of time that the military personnel spend on the base on land and would not include the time on a vessel or a ship.

MODERATOR: Thank you.

Background: The regulations at §630.10(f)(2) Blood Pressure state "A donor with measurements outside these limits may be permitted to donate only when the responsible physician examines the donor and determines and documents that the health of the donor would not be adversely affected by donating." Under §§630.5(b)(1)(i)(A) and (c)(1)(i)(A)(1), the responsible physician is not authorized to delegate this examination and determination of the health of the donor and must personally perform this examination and determination.

Many hereditary hemochromatosis and testosterone therapy donors present to centers or mobile sites where there is not a physician present. They are either deferred or collected as a therapeutic phlebotomy and discarded as a result of an elevated blood pressure. These individuals would otherwise qualify as allogeneic donors under an approved variance, with the exception of blood pressure, which in many cases is secondary to their elevated red cell mass.

Question 7: Under what circumstances would FDA consider allowing a trained and competent designee to perform this evaluation OR allow approval by telephonic consultation with the medical director?

DR. ILLOH: Like you mentioned, according to 21 CFR 630.10(a), "A donor is not eligible if he or she is not in good health, either because of practices that would adversely affect the health of the donor or the product." Then we've already talked about §630.10(f)(2) that includes a physical assessment, including a blood pressure measurement.

Now, under this regulation, we do say that, if the blood pressure exceeds or is below the limits that we've established in the regulations, that a physician can examine the donor and determine if the donor can donate. So, we do allow that. You do not have to discard the unit, if a physician examines the donor and declares that the donor is healthy enough to donate. Just wanted to clarify that. However, we have §630.15 that talks about other requirements for blood donors. Here, we talk about the hereditary hemochromatosis donors and also that applies to the

testosterone donors. They can have their blood collected for allogeneic use, provided they are determined to be eligible under §630.10. They have to meet the requirements of §630.10 also, and that includes blood pressure. And once again, you can have a physician examine the donor and determine that they can donate if their blood pressure exceeds those limits.

Now, we're asking whether someone else, other than a physician, can do that. Maybe I can explain why we put this requirement there. And this is explaining our preamble to the rule, if you look at it.

Basically, in a short form, blood pressure measurements outside the established ranges might be an indicator of a condition that could impact the donor's safety. We maintain that the responsible physician must examine the donor to determine that the donation will be safe. This cannot be delegated.

MODERATOR: Thank you.

Background: The FDA December 2007 guidance *Collection of Platelets by Automated Methods, Section* III, B.1. states:
"For any collection facility that cannot test a pre-donation sample for a platelet count (for example, a mobile collection site), you may use an average of previous historic platelet counts (as specified by the device manufacturer), or a default platelet count (either as recommended by the automated blood cell separator device manufacturer, or determined by using blood center specific values), to set the target platelet yield. You should not collect a triple Platelets, Pheresis from first-time donors who do not have a pre-donation platelet count available either prior to or immediately following initiation of the collection procedure. You should defer from donation donors whose platelet counts are less than 150,000 platelets/uL until a subsequent pre-donation platelet count indicates that the donor's platelet count is at least 150,000 platelets/uL." Based on the guidance, it is possible that a sample, collected on a mobile drive from a first-time donor with no historical platelet count, could show the donor had less than 150,000 platelets/uL when tested after the collection is complete.

Question 8: Would such a collection be suitable for labeling and distribution if it meets all other requirements?

DR. STORCH: The answer is yes; such a collection would be suitable. As per 21 CFR 640.21(d)(1) and (2) and FDA's 2007 Guidance, "Collection of Platelets by Automated Methods", you must assure a pre-donation count of at least 150,000 platelets per microliter. However, if there are no records of a donor's previous platelet count from prior donations and you are unable to assess the donor's platelet count prior to or immediately following the initiation of the collection, you may collect platelets by plateletpheresis.

However, you must not collect 9×10^{11} or more platelets from that donor. In addition, you must defer a donor whose pre-donation platelet count is less than 150,000 platelets per microliter until a subsequent pre-donation platelet count indicates that the donor's platelet count is at least

150,000 platelets per microliter. And you must take appropriate steps to assure that the donor's intended post-donation platelet count will be no less than 100,000 platelets per microliter.

MODERATOR: Thank you.

Background; Regulations at 21 CFR 606.122 describe requirements for the *Circular of Information* as an extension of labeling and state:
"A circular of information must be available for distribution if the product is intended for transfusion…"

The printed copy is available for purchase from AABB. AABB is not currently providing electronic versions of the COI.

Question 9: What are FDA's expectations of the blood donor centers that must make the hard copy Circular "available for distribution"? Please clarify FDA's expectation for the frequency of and method for distribution of the Circular.

MR. MCBRIDE: Thank you. I'll take this. I just want to give you a brief historical background on this -- on the *Circular* right before I answer this.

The current *Circular of Information was* developed in the '70s to provide for safe handling and administration of blood components and to provide uniform labeling to facilitate regional and interregional sharing of the nation's blood supply. In support of these efforts, FDA issued a guideline for the uniform labeling of blood and blood components, which describes suitable labeling for blood and blood components and then promulgated labeling regulations in 1985.

The information elements were removed from the simplified container label and were included in an instruction in the *Circular*. New cautionary statements and instructions to users were included in the *Circular* when the agency determined that the information was necessary. Because the revised simplified container label was intended for use with the *Circular*, the instruction *Circular* must be available concurrent with the use of the container label.

With that said, the *Circular of Information for the Use of Human Blood and Blood Components* is considered to be labeling. It was developed as an extension of the blood bag container label, because the space on these labels are limited. FDA believes that the *Circular* should be distributed to customers. We believe availability of a hard copy *Circular* should be part of the overall distribution process, in accordance with §606.122, to include distribution on a yearly basis or whenever a change is made to the *Circular* or upon request from your customers. Thank you.

MODERATOR: Thank you. Again, questions on the circular of information. This time, we're looking at a different aspect of the requirements. §606.122 also states, "The circular of information must provide adequate directions for use, including the following information. But let me take a step back for a moment and share some information about the development of this. And anybody that's on the Circular of Information Task Force that's in this room, I would

like to say thank you. A lot of effort goes in to this, and it's a very committed task force. We definitely appreciate their work.

Once they have developed the *Circular*, it is submitted to FDA. They review it and then formally recognize the *Circular* as acceptable to meet the long list of requirements that you can find in §606.122(a)(2)(n). A key thing to note is that each facility would need to come up with this extension of labeling. Through the hard work of the task force and FDA, you have the option to not develop your own and simply use this one as your extension of labeling.

Now, we're going to look specifically at §606.122, which requires the *Circular* to provide information critical to work performed from the point of collection through transfusion. That means blood donor centers, transfusion services, perhaps prescribing physician, nursing staff, et cetera. And again, it's a long list. There are instructions to mix the product. There are various statements. An important one - "Do not add medications to blood." There are descriptions of the various products and their sources. Many statements, warnings, indications, dosage, and instructions for administration are captured in the *Circular*.

Background: The requirements of §606.122 also state:
"The *Circular* of information must provide adequate directions for use, including the following information…"
As you know, this extension of labeling is

- **developed by the Circular of Information Task Force and reviewed and formally recognized by FDA as acceptable to meet the long list of requirements in §§606.122(a)-(n). Specifically, §606.122 requires the *Circular* to provide information critical to the work performed from collection to transfusion, by the blood donor center, transfusion service, prescribing physician, and nursing staff, including:**
    - **Instructions to mix the product before use, to use a filter in the administration equipment**
    - **A statement "Do Not Add Medications" or an explanation concerning allowable additives.**
    - **A description of the product, its source, and preparation, including the name and proportion of the anticoagulant used in collecting the Whole Blood from each product is prepared.**
    - **A statement about testing for RTTIs, and the related warnings.**
    - **The use of the product, indications, contraindications, side effects and hazards, warnings, dosage and administration recommendations for handling and transfusion of…**
    - **Instructions for administration.**

Question 10: What is the purpose of this extension of labeling and what are FDA's expectations for the handling of the *Circular* once received by the transfusion service?

Question 11: Do the requirements of §606.122 apply solely to the blood collection establishments or do the requirements also apply to transfusion services to make the *Circular* available to prescribing physicians prior to and/or at the time of issue?

Question 12: Is it FDA's expectation that the *Circular* be made available at the time of issue for transfusions in a private practice or other setting, and for emergency use if needed during patient transport by air or ground etc.?

MR. MCBRIDE: I'll take this one also. As I mentioned briefly a little earlier, the *Circular of Information* is, again, an extension of the information on the blood bag label and is intended to provide information about the product, including information on how the product is prepared, test results, instructions for use, side effects, and hazards. The *Circular* also contains educational information for the users. For this reason, the transfusion services should be familiar with the information in the *Circular*, including the instructions for use.

FDA believes that the *Circular* should be available for prescribing physicians, transfusionists, and other health care professionals for when questions arise regarding blood transfusion. In the preamble to the final rule in 1985, FDA explained that, "While it is often unnecessary to consult the instruction circular during the routine operation of a transfusion service, the *Circular* is useful in providing necessary information when a question arises concerning characteristics of a blood product or its proper administration." So again, FDA believes that the *Circular* should be available for the distribution to physicians, transfusionists, care givers, and health care professionals in any setting in which questions may arise regarding blood transfusion. If the environment includes blood transfusion, the *Circular* should be available. Thank you.

MODERATOR: Thank you.

Background: The currently approved *Circular of Information* states that thawed cryoprecipitated AHF should be kept at room temperature and transfused as soon as possible after thawing, within 6 hours if it is a single unit (from an individual donor, or products pooled before freezing or prior to administration using an FDA-cleared sterile connection device). The wastage rate for cryoprecipitate is 5% of units distributed (2013 AABB Blood Survey Report).

A study published in the June 2016 Transfusion Journal, by Green et al., showed there were no significant changes in levels of fibrinogen and Factor XIII over 72 hours when stored at room temperature (18-24 C). Currently, cryo is issued for fibrinogen replacement and not used as a Factor VIII replacement.

Question 13: What is the process to request that FDA consider updating the requirements to permit room temperature storage (18-24 C) for 72 hours based on current practice for use of cryo for fibrinogen replacement?

Question 14: What data would FDA require to make this change?

DR. STORCH: According to 21 CFR 606.122(n)(5), cryoprecipitated AHF can be stored for no more than 4 hours after entering the container or after pooling, and within 6 hours after thawing. Blood establishments wishing to extend the dating of this product would need to request an exception or alternative to the requirements, under §640.120. FDA would expect the following for consideration of the variance approvals.

First, supporting studies to conclude that fibrinogen levels meet or exceed expected levels; second, robust sterility studies, which should include spiking studies to assess the potential risk of bacterial contamination arising from extended storage at ambient temperature; and third, appropriate labeling, for example, say, "For Fibrinogen use only," including revision of the *Circular*. It's important to keep in mind that relabeling would make the transfusion service a manufacturer. Therefore, registration with the FDA would be required.

MODERATOR: Thank you.

[screen failure] This would probably be a good time to say you'll be able to find these slides and a transcript of this session on the AABB web site. (laughter) On the home page, you would look at the Advocacy tab, hit that, and open up the Regulatory Affairs page. We will have information that you'll be able to find there. You can look for the quick links over to the right margin.

Background: The current *Circular of Information*, states "Do not refreeze after thawing" for Cryoprecipitated Components.

Question 15. Is there an FDA approved pathway which allows for the thawing of previously manufactured and frozen individual cryoprecipitate components, pooling by an FDA-cleared sterile connection device and refreezing of the pooled component if not transfused?

DR. STORCH: The answer is no, we do not consider this product to be manufactured, in accordance with current cryoprecipitate regulations, specifically, §606.122(n)(5), which says, "Store at room temperature after thawing and begin administration as soon as possible but no more than 4 hours after entering the container or after pooling and within 6 hours after thawing, as well as §640.54 regarding maintenance of sterility so as not to have an adverse effect on the safety, purity, or potency of the final product."

MODERATOR: Thank you.

Background: Section 600.15 describes temperatures requirements for shipment of Red Blood Cells "1-10 C."

Question 16: Does FDA allow a temperature range of 1-10 C for all red cell shipment containers (coolers) regardless of whether the container is in transport or serving as temporary storage?

Question 17: Or does FDA require a temperature range of 1-6 C if the container is not in transit?

MS. CIARALDI: Okay, I'll take this one. Just so you thought that I wasn't only up here just to make the panel look good. They said I had to earn my keep. We do get this question a lot, and I'm pretty sure I understand the confusion. But I hope my explanation will help. Let's start by reviewing the applicable regulations. In addition to the one that's listed, there are two others.

They are§640.11(a) and §610.53(b). Both of them require the red cells to be maintained between 1- 6 C during storage. §615(a) requires the red cells to be maintained between 1- 10 C during shipment. But the question is really about storage. So, let's talk about that.

The regs require the red cells to be stored between 1-6 C, regardless of where they're stored, whether it be in the blood bank or in the operating room and regardless of which device is used to store the red cells, whether it be a refrigerator or a cooler. Now, we all know that red cells are normally stored in a blood refrigerator that's been validated to maintain the temperature at 1- 6 C. But there are certain situations where coolers are used for temporary storage.

In those situations, the storage containers, even though they're used for temporary storage, must be qualified for their intended use. According to regulations, the intended use is that the red cells be maintained at 1- 6 C. The qualification of the temporary storage containers, regardless of what they are, should include ensuring that they will maintain the proper temperature for the timeframe that's specified in your procedures.

In summary, if a shipment cooler is used for storage, it must be able to maintain the red cells between 1 - 6 C for the maximum time it could be used for storage. If the shipment coolers are used to transport the red cells from one location to another, they must be able to maintain the red cells between 1-10 C during the maximum possible shipment time. Thank you.

MODERATOR: Thank you.

Background: Section 630.3(e) defines an infrequent plasma donor as a donor who has not donated plasma by plasmapheresis or a co-collection of plasma with another blood component in the preceding 4 weeks. FDA's 2007 Guidance Collection of Platelets by Automated Methods defines a Concurrent Component as follows: "When a blood component, such as Platelets, is being collected during an apheresis procedure, a concurrent component is a different blood component (i.e., Plasma, RBCs) collected at the same time."

Question 18: Do these two definitions refer to the same product?

Question 19: What would be the appropriate name for the plasma product produced by the removal of plasma from an apheresis platelet during the manufacture of a Platelet Additive Solution Platelet? Co-collected, concurrent or something else?

MR. MCBRIDE: Yes. (laughter). The terms co-collection and concurrent component both refer to the collection of separate blood components during the same apheresis procedure. A separate unit of plasma collected during a plateletpheresis and/or a red blood cell apheresis procedure is considered a co-component or a concurrent component.

Regarding the second question, it's something else. (laughter) These donors are considered platelet apheresis donors. Therefore, the collected platelet product should comply with appropriate 21 CFR 640.20 series regarding platelet manufacturing regulations. The plasma removed from an apheresis platelet product and replaced in part with a platelet additive solution

can either be returned to the donor or retained as a separate plasma product, but it is not considered a plasma co-component, since it is prepared afterwards from the collected platelet product.

The final product name depends on how the plasma product is processed after collection, in accordance with §640.30 series on plasma products. For example, time to place in the freezer, the intended use. In other words, is it for transfusion or for further manufacture? So, it could potentially be labeled FFP, PF24, PF24/RT24, or even recovered plasma. Again, the FDA does not refer to these plasma products as co-components, since they are not actually directly collected from the donor during the manufacturing process. Thank you.

MODERATOR: Thank you.

Background: The package insert for bioMérieux culture bottles states that the inoculated bottle should be placed on the BacT/ALERT analyzer as soon as possible. Some reference laboratory instructions allow up to 48 hours (possibly longer?) for transport.

Question 20: How is the phrase “as soon as possible” defined? Is 48 hours acceptable if there is a validation? Does the manufacturer or FDA have to approve this?

MS. CIARALDI: Okay, I'll take this one. As noted, the current bioMérieux BacT/ALERT microbial detection system package inserts state, "Inoculated bottles can be placed in the incubator as soon as possible after collection." The package inserts do not specify a maximum time limit between inoculating the bottles and placing it in the incubator. I did a little looking around on this, and I did find some additional information.

The manufacturer, bioMérieux, does provide this information on their website and I gave the web site to Sharon. She'll include it in the transcripts.

The information emphasizes clinical laboratory recommendations based on the principal of the test. I'm going to quote from this website. "Inoculated bottles should be transported to the laboratory for testing as quickly as possible, preferably within two hours per CLSI, which is (Clinical and Laboratory Standards Institute)." It goes on to say, "Any delay in testing the inoculated bottles may potentially lead to an increased risk of false negative results. If you expect to have delays in placing the inoculated bottles in the incubator, you should contact the test system manufacturer for instructions."

To summarize this response, the intention of the instructions is to ensure that there's no delay in getting the inoculated bottles into the incubator because of the effect it could have on the sensitivity of the test. If delays are expected for this particular test, the blood establishment should contact bioMérieux for specific instructions on what to do in this situation. Thank you.

MODERATOR: Thank you.

Background: Section §606.145(c) states: In the event that a transfusion service identifies platelets as bacterially contaminated, the transfusion service must not release the product

and must notify the blood collection establishment that provided the platelets. The transfusion service must take appropriate steps to identify the organism; these steps may include contracting with the collection establishment or a laboratory to identify the organism. The transfusion service must further notify the blood collection establishment either by providing information about the species of the contaminating organism when the transfusion service has been able to identify it, or by advising the blood collection establishment when the transfusion service has determined that the species cannot be identified.

Question 21: With the delay of the final guidance, please clarify if there are any *current* requirements to perform a culture and ID if a transfusion service is using Verax bacterial detection test for platelets and has a repeat positive unit.

MS. CIARALDI: Even though the final guidance hasn't been issued yet, there are current requirements that are in the regulations for transfusion services related to performing a culture and identifying the organism. I'm going to repeat a little bit what's on the slide, but I like to bring in the regs in their full context.

The applicable regs to this particular question are §606.145(a), which states, "Blood establishments and transfusion service must assure that the risk of bacterial contamination of platelets is adequately controlled using an FDA-approved or cleared device or other appropriate or adequate method that FDA has found acceptable."

Then on to §606.145(c). It states, "In the event a transfusion service identifies platelets as being bacterially contaminated, the transfusion service must not release the product and must notify the blood collection establishment that provided the platelets. The transfusion service must also take appropriate steps to identify the organism. This can be done through a contract with the collection establishment or another laboratory. Then the transfusion service must notify the blood collection establishment of the species of the contaminating organism or tell them if the species cannot be identified." And one last reg. I love regulations, but then I have no life. This is why I use them a lot. §606.65(e) requires supplies and reagents to be used in a manner consistent with the manufacturer's instructions. And you'll probably wonder why I included that, and that's on page 2. The 2017 Verax biomedical platelet PGD test package insert, or the manufacturer's instructions, states the following. "When repeatedly reactive doses are found, notify the platelet provider and determine appropriate follow-up action, such as confirmatory culture and bacteria identification."

To summarize, if a transfusion service tests platelets with the Verax test and finds a repeat reactive unit, it must culture the unit, identify the organism, and notify the collection establishment of the species or if the species can't be identified. The culture and identification can be done by a contractor.

You may be asking, “If everything's covered in the regs why do we need the guidance?” The guidance helps explain the requirements and also advises collector and transfusion services how they can comply with the regulation. Thank you.

MODERATOR: Thank you.

Background: The FDA's December 2007 guidance, Collection of Platelets by Automated Methods, states in Section IX, Labeling, that:

- **Container labels must comply with §§606.121 and 610.60. In addition: Platelets, Pheresis components for transfusion, containing less than 3.0 x 10^{11} platelets per storage container, should be labeled with the actual platelet content.**

How does is this applied to platelet collections containing less than 3.0x10^{11} in the following examples:

Question 22: For a collection with a yield of 4.5x10^{11} platelets that is split into three 1.5 x 10^{11} yield platelet products for neonatal or pediatric use, would the original product be qualified at greater than 3.0 x 10^{11} and the three splits be labeled with the actual yield?

Question 23: For a collection that never qualified at a yield of 3.0 x 10^{11} because the donor ended to donation early without problems, with a yield of 2.8 x 10^{11}

MS. CIARALDI: The 2007 plateletpheresis guidance document says -- again, I'm going to repeat a little bit. "Plateletpheresis for transfusion should routinely contain greater than or equal to 3 x 10^{11} platelets." It also says, "When special circumstances warrant their use, plateletpheresis components containing less than 3 x 10^{11} should be labeled with the actual platelet content."

For the first question, the platelet component with the yield of greater than or equal to 3 x 10^{11} should be labeled as a regular apheresis platelet. It can be subdivided if smaller doses are needed for pediatric transfusions. It is not required for the pedi-units to have the actual platelet content on the label. However, §606.121(c)(5) requires the label of the pedi-units to include the product volume.

For the second question, a platelet component with a yield of 2.8 x 10^{11} should be labeled as a low-yield apheresis platelet. As stated in both the 2007 guidance and in the March 2013 "Consensus Standard for a Uniform Labeling of Blood and Blood Components", using ISBT 128, the actual platelet yield should appear on the label of these products. In summary, with the exception of the pediatric doses made from apheresis platelets, apheresis platelet components with less than 3 x 10^{11} platelet should be labeled as low-yield. However, the pediatric doses must have the product volume on the label. Thank you.

MODERATOR: Thank you.

Background: AABB sent out a survey to members and submitted a second set of comments to the docket for the March 2016 Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion. In the updated Guidance Agenda for 2017, FDA stated: "Taking into account public comments, we are considering discussing the topic at a future Blood Products Advisory Committee meeting and intend to issue a revised draft guidance in 2018."

Question 24: As more hospital transfusion services are recognizing the impact of recommendations for risk control strategies, will the FDA be re-opening the comment period for the Draft Guidance?

DR. ILLOH: Just as we all know, I think there's been a lot of discussion at this meeting about bacterial contamination of platelets and its risk to recipients. We take this issue very seriously, and we know there are a lot of moving parts, in terms of how to mitigate this issue. Hence, our need to discuss this issue further at an advisory committee meeting, but also to revise the guidance and supply a draft guidance again.

Now, I'm encouraging all stakeholders -- not just blood collectors, but also transfusion services or anybody else who is engaged in this issue to look at the draft guidance that is already published now and submit comments to us. We do look at all the comments, and it helps us develop our policies about this issue. Concerning the docket, we don't intend to formally reopen the docket, but it's technically still open. You can always talk to us anytime. There are different avenues.

For this one, you can submit your comments on the March 2016 draft guidance at any time. Comments should be submitted to docket FDA-2014-D-1814. I'll give this to Sharon so she can put this on the transcript. It's also on the web site https://www.regulations.gov/.

FDA has received numerous comments already on the draft guidance, very helpful comments, new data, since the comment period closed in 2016. But we will still look into the docket for more comments. We also got comments from the American Hospitals Association, and the comments have been posted to the docket. You can also actually look in there to see what people have said.

As Sharon mentioned, we do plan to discuss this topic at a future Blood Products Advisory Committee meeting. Look out for our Federal Notice announcing the time and dates for that meeting. We will also welcome comments during the open public hearing.

For those of you who have not gone to our advisory committee meetings, we do give time for the public to speak, present data, or give their thoughts about the implementation issues, operational issues, data that we may not be aware of. So, you will have that opportunity. You just have to follow the process to let us know that you will be coming to talk.

And we intend to issue a revised draft guidance, again, for public comment in 2018. So more to come with this issue. Thank you.

MODERATOR: Thank you.

AABB will be participating and submitting -- compiling comments to submit yet again. I would encourage you to go ahead and act on your own behalf. You have a voice through the docket, but you can also send it to regulatory@aabb.org.

Background: Many apheresis centers use Terumo BCT devices. Terumo BCT has decided to sunset their older model COBE Spectra at the end of calendar year 2017, despite the fact that they do not have FDA approval for leukoreduction and platelet apheresis on their newer model Spectra Optia.

Question 25: Who can we contact at FDA to discuss how best to continue to provide necessary care of leukoreduction and platelet apheresis without FDA-approval for these indications and no other alternative devices?

MS. CIARALDI: I'll take this one. Blood components used for transfusion or for further manufacturing must be collected on FDA-cleared instruments that are labeled to collect and make the blood components. The Spectra Optia is cleared by our Center for Devices and Radiological Health for therapeutic apheresis procedures, such as plasma and red cell exchange, white blood cell and platelet depletion procedures, bone marrow processing, and the collection of mononuclear cells and granulocytes.

It is not cleared by my center, CBER, Center for Biologics, Evaluation, and Research. It's not cleared for the collection of platelets, red blood cells, and plasma used for transfusion. We are aware that there are other apheresis instruments that are cleared by CBER for the collection of blood components, such as, again, platelets, red cells, and plasma from blood donors. In summary, the Optia cannot be used for collecting platelets, red cells, or plasma intended for transfusion or for further manufacturing. If you intend to continue collecting apheresis platelets, including leukocyte-reduced apheresis platelets, you will have to transition to one of the other FDA-cleared apheresis instruments.

MODERATOR: Thank you.

For this question, it became very clear to us at AABB, as we were looking at input from our members. Many of you are getting an increase in the requests for very creative new products or collections of some different type than you've done before. Those questions were really very broad in the range. When we submitted it to FDA, it was already clear to us, but FDA confirmed that they really need to speak with you about details of your specific product.

Were they to give an answer today about one example that was submitted for this session, it would not apply to another example, and that would lead to a lot of confusion and misinformation. We don't want to do that.

Please contact the manufacturer's assistance and technical training branch at CBER, specifically, the Division of Manufacturer's Assistance and Training, Office of Communication, Outreach, and Development. These people are there to help you get answers to your questions. We have the address here, and I'm sure you can Google that and also phone numbers and email at industry.biologics@fda.hhs.gov. I would encourage you to get that information specific to your needs.

Now, before we move on to our questions on cellular therapy, Rick McBride and Safa Karandish would like to say a few words about the registration and listings rule that was issued last year.

MR. MCBRIDE: Thank you. In August 2016, FDA published a final rule that amended FDA's regulations governing drug establishment registration and listing. The final rule includes a few changes to the requirements of both blood product establishments as well as human cell, human tissue, and cellular and tissue-based product establishments to register.

Regarding blood products, these new requirements are now defined in 21 CFR Part 607, entitled, "Establishment Registration and Product Listing for Manufacturers of Human Blood and Blood Products and Licensed Devices," starting with the April 1st, 2017 edition of the CFR. But just to summarize, registration of blood product listing must be submitted electronically now through the Blood Establishment Registration and Product Listing System or any future superseding electronic system. Establishments must register annually now between October 1st, as opposed to November 15th, and December 31st by accessing the FDA web site.

And firms that engage solely in the manufacture of plasma derivatives are now exempt from registration under 21 CFR 607. They must still register under 21 CFR 207 as biologic drug manufacturers. So, right now, right after this session, you can go out and click on the FDA web site and start registering. You don't have to wait any more until November 15th. Now I'm going to turn it over to Safa for follow-up on this issue as it relates to human cells, tissues, and tissue products. Thank you.

MS. KARANDISH: Good morning. So, this final rule also requires HCT/P establishments to submit their registration and product listing information electronically. Manufacturers of 361 HCT/Ps must continue to register and list their products, according to 21 CFR Part 1271, using the electronic HCT/P establishment registration system, or eHCTERS. I believe many of you are already using that system to submit your registration information.

There are also some new requirements for foreign establishments that register and list with the FDA. You can find all the registration requirements in Subpart B of the 1271 Regulations. Beginning November 29th of this year, paper registration forms will no longer be accepted.

Additionally, under this final rule, manufacturers of HCT/Ps that are regulated as drugs, devices, and/or biological products must register and list their product, according to Parts 207 or 807, as applicable, rather than Part 1271. Just as a reminder, establishments that only manufacture investigational products, under an IND (Investigational New Drug Application) or IDE (Investigational Device Exemption), are not required to register with the FDA until their product is licensed, approved, or cleared. FDA is in the process of updating the CBER blood and tissue registration web sites, and you can refer to these web sites in the near future for additional information.

MODERATOR: Thank you. At this time, we're going to move to questions on cellular therapy, and I'm going to turn this over to Karen Palmer.

MS. PALMER: Good morning. It's my pleasure to introduce Safa Karandish. She's the Consumer Safety Officer in the Office of Tissue and Advanced Therapies and she will be answering the cellular therapy questions.

Background: With reference to Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products-Draft Guidance, October 2015, and 21 CFR 1271.3(c), *Homologous use* means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.

Question 26: Will FDA define the term "Homologous use" as it relates to experimental cellular therapies to treat brain or solid organ disease, whether the cell source for administration (under an IND) is allogeneic mesenchymal stromal cells (MSC) from adipose, placenta or cord blood?

Question 27: How does FDA regulate and/or does FDA regulate platelet rich plasma (PRP) when collected as part of same day surgical procedure such as in the orthopedic setting?

MS. KARANDISH: The first question is related to FDA's regulatory framework for HCT/Ps. 21 CFR Part 1271.10(a) provides the 4 criteria that an HCT/P must meet for regulations solely under Section 361 of the Public Health Service Act and the regulations in Part 1271. HCT/Ps that meet all four criteria are not subject to pre-market review requirements. These are the so-called 361 HCT/Ps.

HCT/Ps that don't meet the four criteria are regulated as drugs, devices, and/or biological products under Section 351 of the PHS Act and/or FD& C Act. This group of products are subject to the pre-market review requirements. One of the criteria for an HCT/P to be regulated solely under Section 361 is that the HCT/P must be for homologous use only.

Homologous use is defined in the regulation and as it was referred in the background section of the question, you can find that definition in 1271.3(c). I think many of you are aware that FDA has published a draft guidance related to this topic as well as other guidances, draft guidances, related to the Subpart A of the 1271 Regulations. The public comments that have been submitted to the agency are currently under consideration, and it remains a priority for FDA to finalize these guidances before the end of this year.

If you have product-specific questions concerning the applicable regulations and jurisdictions, you can submit those questions to the Tissue Reference Group. And the email address is tissuereferencegroup@fda.hhs.gov.

Now, regarding the second question, platelet-rich plasma does not meet the definition of an HCT/P. Therefore, the 1271 Regulations don't apply to PRP. The inquirer can contact Manufacture's Assistance and Technical Training Branch at CBER for additional information. Their email address, as it was mentioned earlier, is industry.biologics@fda.hhs.gov.

MS. PALMER: Thank you.

Background: Cord blood banks may collect and store a variety of cells and tissues from umbilical cord blood, cord tissue, or placenta for some future application in first or second-

degree relatives. Currently, there is variability in the practices across these services and many products do not have a specific indication at the time of storage, such as mesenchymal stromal/stem cells which are of interest in the evolving fields of cellular therapy, immunotherapy, and regenerative medicine. Various regulations including 21 CFR 1271.10, PHS 351 and 361 apply.

Question 28: As these downstream applications evolve, does the agency have any guidance or suggestions for processing umbilical cord tissue MSC prior to storage that would make them the most broadly applicable at a later time?

Question 29: Is there a preferred approach or method of processing (tissue fragments, digested tissue with cell isolation, limited cell expansion, other)?

Question 30: Conversely, are there any processing methods (tissue fragments, digested tissue with cell isolation, limited cell expansion, other) that would push them beyond 'minimally manipulated'?

MS. KARANDISH: All of these questions are asking about the options for long-term storage of different gestational tissues from family-related donors for potential future unidentified uses, and the questioner is asking FDA whether we have any preferred method for processing such products. FDA does not have a preferred method of processing. It's up to the manufacturer to define the method that they want to use. It is important for HCT/P establishments to know that if the manufacturing or future use of stored HCT/Ps will not meet all the criteria in 1271.10(a), then the product would be regulated as a drug, device, and/or biological product, which means that you would need to comply with the applicable 1271 Regulations and all regulations applicable to drugs and biological products. Now, regarding the minimum manipulation criteria, FDA has published a draft guidance on this topic, and you can refer to that guidance for more information.

MS. PALMER: Thank you.

Background: According to AABB Standards, materials that come into contact with the patient or cellular therapy product shall be sterile and of appropriate grade for the intended use and, whenever possible, shall be approved for human use by the United States FDA or relevant Competent Authority. For cell therapy product collection and processing, all supplies must be certified as sterile.

In the November 2013 Drug Safety Communication titled, *FDA requests label changes and single-use packaging for some over-the-counter (OTC) topical antiseptic products to decrease risk of infection*, several points were made:

- **When used properly, OTC topical antiseptics are safe and effective products to reduce the number of bacteria on the skin prior to surgery or an injection.**
- **To reduce the risk of infection, ensure the products are used according to the directions on the label.**
- **OTC antiseptics packaged in single-use containers should only be applied at one time to one patient.**

• All topical antiseptics are required to be manufactured under Current Good Manufacturing Practice (cGMP) regulations, which require manufacturers to have appropriate procedures in place to prevent the presence of objectionable microorganisms in drug products that are not manufactured as sterile.
•A "nonsterile" label does not mean the product contains harmful bacteria, but rather that its contents have not been sterilized, or treated with a process during manufacturing to eliminate all potential microorganisms.

Question 31: It has been difficult to find single use chlorhexidine swabs, povidone iodine swabs, etc. available and certified as sterile, what should the facility do?

MS. KARANDISH: Considering the background information, the question is whether single-use antiseptic swabs that are used during manufacturing, for example, recovery of HCT/Ps, must be labeled as sterile. For 361 HCT/Ps, the requirements for supplies and reagents are defined in the Current Good Tissue Practice Section of the 1271 Regulations. These regulations do not require that supplies be labeled as sterile.

However, as required under 1271.210(a), you must not use supplies and reagents until they have been verified to meet specifications designed to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable diseases. In the 2011 cGTP guidance, cleaning swabs are described as one example of a supply that is used during HCT/P manufacturing. This guidance explains that HCT/P manufacturers may use the vendors' certificate of analysis to verify that the relevant specifications are met. But please note that the AABB standards or other accreditation standards may have additional requirements regarding supplies that are used in manufacturing. For supplies or other components used for manufacturing HCT/Ps that are also regulated as drugs or biological products, you would need to refer to the cGMP requirements in 21 CFR Part 211. Thank you.

MS. PALMER: Thank you.

Question 32: Please clarify what constitutes a closed system? For example, if a syringe is used to aseptically access a vial of cryoprotectant inside a laminar flow hood and attached to a 0.2-micron filter, which is part of a kit, is that still considered a "closed system"?

Question 33: Does the FDA approval of the Sepax Cell Separation System absolve a facility from final sterility testing after this step?

MS. KARANDISH: Okay, the steps that are described in the first question, which includes connecting a syringe that contains a cryoprotectant solution to a 0.2 micron filter inside a biological safety cabinet, are considered good aseptic practice, rather than a closed system. Now, regarding the Sepax System, this device has been cleared by the FDA for processing cord blood using a compatible single-use separation kit that is supplied by the device manufacturer. However, use of this system does not necessarily mean that the cord blood manufacturers are no longer required to comply with the applicable processing controls and testing requirements to ensure that the products that they manufacture are not contaminated. It is important to note that, depending on how a piece of equipment or a device is used in manufacturing, the product may

become contaminated during handling, different manufacturing steps, or it is also possible that the incoming material may have been contaminated before processing.

Using the specific equipment or an instrument could provide a level of assurance from contamination that could occur during processing steps. However, proper controls, including QC testing, is still necessary for releasing the final product.

MS. PALMER: Thank you.

Background: Voluntary standards, regulatory requirements and best practices indicate the need to label the contents of the container. For certain ancillary materials used for biopreservation, such as CryoStor media, the package insert provides a partial list of ingredients, excluding the proprietary cryopreservation material. The company has a drug master file (DMF) on file with FDA and the package insert lists only some of the ingredients due to the proprietary nature. The manufacturer states their customer service and scientific staff are available to consult with physicians as needed. Most facilities label these as HPC, XXX in CryoStor with 10% DMSO.

Question 34: Based on the above scenario, is this sufficient from an FDA perspective?

MS. KARANDISH: As I understand, this question is asking whether the name of all additives or ingredients in the cryoprotectant solution must be included on the HCT/P label. For 361 HCT/Ps, the labeling requirements are defined in 1271.370. This provision provides a list of information that must be included on the HCT/P label, including a description of the type of HCT/P.

But there is no specific requirement for including information about additives or other ingredients on the product label. Again, AABB standards may have additional requirements regarding information that must be included on the label. The 1271 Regulations includes requirements for supplies and reagents that are used during manufacturing. And as I explained earlier, you must not use supplies or reagents until they have been verified to meet the relevant specifications.

Now, for HCT/Ps that are regulated as drugs, devices, and/or biological products, there are specific requirements for information that must appear on the container and the package label. And these requirements are in 21 CFR Part 610. For this group of products, the content of the labeling is reviewed by the FDA. And additionally, during the review of an application, the agency reviews the information about all reagents and components that are used in the manufacturing of the product.

MS. PALMER: Thank you.

Background: Blood centers and cell therapy service providers receive a variety of requests for the collection of HCT/P, such as apheresis, for future use in which the specific intended use is not clear or not specified. These requests currently come primarily from cosmetic surgeons. Sometimes the patient treatment is intended to take place outside of the US and the requisition includes export of the product to another country. Secondly, facilities are

sometimes approached by individual customers who want to collect and store any variety of autologous cell or stem cell sources for unspecified future use, such as for regenerative (anti-aging) purpose. The business office often views this as a typical fee for service activity.

Question 35: As a manufacturing facility that performs the collection, storage, or export of such products, what regulations apply and what liability exists?

Question 36: What additional responsibilities apply to facilities providing these support services?

Question 37: If a customer discovers the cells are not usable for a future technology or application after many years of storage, what are the responsibilities of the facility?

MS. KARANDISH: These questions are similar to an earlier one, and they're all about HCT/Ps that are manufactured and then stored for potential future unidentified uses. Now, first I have to mention that we cannot answer questions about liability, future responsibility, and responsibilities of the facility if the cells are not usable in the future.

Storage of products that were mentioned in this question are held to Part 1271 requirements, including requirements for registration, and listing and these facilities are subject to FDA inspection. It is important for the establishments to be aware that, if the manufacturing or future use of the stored HCT/Ps will not meet all the criteria in 1271.10(a), then the product would be regulated as a drug, device, and/or biological product, as I explained earlier. This would mean, among other things, you would need to comply with the applicable 1271 Regulations and all regulations applicable to biological products.

Regarding HCT/Ps intended for export, questions regarding a specific product situation should be emailed to cberimportinquiry@fda.hhs.gov.

MS. PALMER: Thank you very much.

Background: Many previously stored public cord blood units do not meet current donor or product specifications. The consent indicates these units may be released for research or further manufacture.

Question 38: What is FDA's current thinking on the sale or release of HCT/Ps for "further manufacture"?

Question 39: Could these remanufactured products be used for human transfusion, transplant, injection, topical application, or other similar uses?

Question 40: Are these allogeneic products safe if they have met donor suitability requirements and cGMP manufacturing standards (as applicable) if used for human transfusion, transplant, injection, topical application, or other similar uses?

MS. KARANDISH: These are all very broad questions, and we cannot provide responses without more specific information about the products and their intended uses. As I explained earlier, if an HCT/P meets all the criteria in 1271.10(a), then it will be regulated as a 361 HCT/P, and you must comply with the 1271 Regulations, which include the requirements for registration and listing, donor eligibility determination, and the current good tissue practice. Those HCT/Ps that don't meet all the four criteria are also regulated as drugs, devices, and/or biological products, and manufacturers of these products must comply with the 1271 Regulations, as well as the cGMPs and the device quality system requirements, as applicable.

MS. PALMER: Thank you.

Background: The regulations of 1271.10(b) and Draft Guidance for Industry, *Human Cells, Tissues, and Cellular and Tissue-Based Products from Adipose Tissue: Regulatory Considerations,* address facility registration.

Question 41: When registering with FDA, a facility that collects and processes adipose tissue can note this type of collection on the establishment registration. However, the public query function on the FDA website does not have a search option for adipose tissue. Could FDA please add this?

Question 42: Is it the expectation of FDA that all surgery facilities performing adipose related procedures, such as fat grafting, register with FDA?

MS. KARANDISH: Okay, regarding the first question, it is correct that our current HCT/P registration public query application does not allow you to search for establishments that have registered for manufacturing certain types of HCT/Ps, and adipose tissue is one example. We will consider improving the search functionality in the future versions of the application.

Now, regarding the second question, that answer depends on how the adipose tissue or any other HCT/P is regulated. Unless one of the exceptions under 1271.15 applies, you need to consider the regulatory framework and determine whether the HCT/P meets all the criteria for regulation solely under Section 361 of the PHS Act. Thank you.

MS. PALMER: Thank you. And with that, I will turn it back over to Sharon for the ask the CMS/CLIA questions.

MODERATOR: So again, I'd like to thank Kathy Loper and Jessica Yozwiak for helping prepare those questions for submission to Safa. And thank you, Safa.

Penny Meyer can't be here. As I said, she was gracious enough to provide responses to the questions.

Background: We are a large multi-hospital system that shares our transfusion service computer system across all our hospitals.

Question 43: For surgical outpatients, is it acceptable to perform a type and screen under one CLIA license and then perform an electronic crossmatch under another CLIA license (when the patient qualifies for an electronic crossmatch)? If this is acceptable, are there any other aspects to consider in adopting such a process?

And Penny's response is that "CLIA does not prohibit this practice. Both facilities must follow 42.493.110, which states that the facility must establish and follow policies to ensure positive identification of a blood or blood product recipient."

Question 44: Please clarify the January 7, 2011, CMS Memorandum to State Survey Agency Directors, *Clinical Laboratory Improvement Amendments of 1988 (CLIA)—CLIA Applicability for Laboratory Testing Associated with Blood, Cells/Tissue, and Organs,* as it applies to the following:

Is sterility testing performed by a cord blood bank on the collection considered patient testing that is subject to CLIA, or is it considered a product quality control test? If it is not subject to CLIA, does the cord bank need a CLIA certificate to perform such sterility testing?

And Penny says, "Per the reference memorandum, CLIA applies to sterility testing for those facilities with donor notification policies. The laboratory must have a CLIA certificate in order to perform the testing."

Background: There are increasing reports of blood centers who received a nonconformance related to the laboratory director's delegation of competency assessment of testing employees.

Question 45: To whom (with what level of qualifications) can a Laboratory Director delegate this assessment to, for moderate and high complexity testing? Does it vary by test system/type, or just by test complexity rating?

And Penny's answer is, "The requirements for delegation vary according to test complexity. The technical consultant for moderate complexity testing is responsible for performing and documenting competency assessments. The competency assessments may also be performed by other personnel who meet the regulatory qualification requirements for technical consult for moderate complexity testing."

Question 46: For competency assessment, what is the definition of "annually thereafter"? Is the annual date 12 months from the date of the last competency assessment performed in the first year?

And Penny's answer to this is, "Per CFR 493.1413 and 1451, competency assessment must be performed annually starting from the time the individual starts testing patient specimens." So that's your start date.

Question 47: Is it acceptable to change the annual competency assessment date in order to lessen the number of dates to track?

Penny's answer is, "The competency assessment dates may change, as long as the requirement for annual competency assessment is met."

Background: 42 CFR 493.1451(b)(9), which states that the technical supervisor (of any specialty) will perform competency evaluation semiannually during the first year and annually thereafter. It allows delegation to a general supervisor in §493.1463(b)(4). This allows delegation of the annual competency evaluations, but it doesn't say semi-annual.

Question 48: For the 6-month competency evaluation, would a general supervisor be able to do that evaluation?

And Penny's response is, "Although not specified in the regulation, we have allowed the general supervisor to perform the semi-annual evaluations."

Background: It is well understood that the CLIA regulations do not apply to cell therapy product testing, except for microbial testing if results are reported. However, the CMS document S&C-11-08-CLIA does not address patient testing for CD34 counts.

Question 49: Do CLIA regulations apply to patient peripheral blood CD34 testing?

And Penny's response is, "The scope of the November 2008 document is CLIA applicability for blood, cells, tissues, and organs. CD34 counts on patient specimens are subject to CLIA."

Background: CLIA regulations are considered applicable for microbial testing of cellular therapy products if the results are reported to the patient or physician as required by AABB Standards. If the testing is detection only what proficiency test would you recommend using? There does not appear to be a CMS approved proficiency test available as there is for platelet apheresis products.

Question 50: Could that proficiency be acceptable to use for CT products also?

"It is the responsibility of the laboratory to determine if proficiency testing for the method and sample type they use is available from a CMS-approved proficiency testing provider. In general, the laboratory contacts the PT providers for this information. It is advisable to maintain a record of this research. If suitable PT is not available, then the laboratory must twice annually verify the accuracy of the test 42 CFR 493.1236 (c)."

And again, we take questions all year long. Please find us at the regulatory@aabb.org or under advocacy for our regulatory affairs web page, look for the slides and the transcripts. It does take us a while for us to get the transcripts back. And then you can imagine there's a lot of confusing words in there that we need to re-identify to make sense. Once we've done that, we will post it on our website.

Thank you so much, to our members who submitted questions. And thank you very much, to our panelists. We appreciate it.