Ask the FDA and CMS/CLIA
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MODERATOR: Welcome to this year's session of Ask the FDA and CMS/CLIA. My name is Sharon Carayiannis. I'm the Deputy Director in Regulatory Affairs at AABB and I'm the moderator for this session. Today I am joined by my colleague Brandon Sandine, Specialist in Cellular Therapies, Regulatory at AABB, and he'll present questions on HCT/Ps. Brandon and I have no disclosures.

ILLOH: Good evening. My name is Orieji Illoh. I just want to take the opportunity on behalf of my colleagues to thank you for coming to attend this session and we look forward to the opportunity to address your questions the best that we can. It's been a busy year for both you and us with -- you know, shall I start listing them?

MODERATOR: Our objectives for this session are to describe FDA blood and HCT/P policies, regulations and inspection programs, describe clinical laboratory improvement amendments, CLIA regulations that are applicable to blood and cellular therapy programs. So, let me just tell you first that we have many questions, which is great, and thank you for submitting them.

Background: The *Circular of Information for the Use of Human Blood and Blood Components* (the *Circular*) is an extension of container labels, as the space on those labels is limited. Under 21 CFR 606.121(c)(8)(ii), the label of products for transfusion must include the statement: "See circular of information for indications, contraindications, cautions, and

methods of infusion."

The April 2014 FDA Guidance*, An Acceptable Circular of Information for the Use of Human Blood and Blood Components,* recognized the November 2013 *Circular* as an acceptable extension of container labels and provided instructions to licensed manufacturers for reporting implementation to FDA under §601.12. The guidance states in Section III: "Any subsequent modifications to the November 2013 Circular are not covered by this guidance."

In addition, Section IV. Implementation, addresses modifications to the *Circular,* describing a modification to the *Circular* as a major change that must be reported "as a Prior Approval Supplement consistent with §601.12(f)(1)."

Question 1:
Under Hologic's IND, we are to ensure that the Circular of Information is updated to indicate "Units labeled as negative for Zika virus RNA were tested with an investigational nucleic acid test (NAT) and found to be nonreactive." We would like to add this verbiage to the pdf and hard copy versions of the *Circular* but need help interpreting the April 2014 Guidance.

- **Are we permitted to add this verbiage to the pdf and hard copy versions of the November 2013 *Circular?***
- **Would a change to the *Circular* to add the information, as required under IND, be a minor change or a major change that would require a PAS?**
- **What is an acceptable location to place the additional information?**

PAUL: I will answer that question.

Good afternoon. The FDA guidance for industry titled, "Revised Recommendation for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components", issued in August 2016 states:

Under 21 CFR 606.122(h) the *Circular of Information* must include the names and results of all the tests performed when necessary for safe and effective use. When testing is performed, we recommend that you update your *Circular of Information* to include the non-reactive ID-NAT result for Zika virus. You should indicate whether the testing has been performed using an investigational or a license test. In regards to the wording, the IND sponsors are providing the proper wording for the circular and you should follow the directions provided by the IND sponsors.

In response to the question about whether this would require a PAS, because you are following the instructions provided by the IND sponsor we would consider this change to be minor and you do not need to submit your circular for our approval. You may include this change in your next annual report.

the final question is, what is the acceptable location to place the additional information. This information should be readily noticeable, but you may decide where in the circular to place your Zika testing information.

MODERATOR: Thank you, Wendy.

Question 2: Following FDA's August 2016 ZIKV guidance, does the FDA continue to require that establishments use language provided in their approved IND for Zika virus testing to update their circular or does FDA expect AABB's Circular of Information Task Force to develop language for the Circular?

PAUL: At the present time, you should just follow the labeling instructions provided by the IND sponsor.

MODERATOR:

Background: Regulations at §606.122 describe requirements for the Circular as extension of labeling and state: "A circular of information must be available for distribution if the product is intended for transfusion."

Question 3: Is it acceptable to provide transfusion services with an electronic copy of the Circular?

PAUL: As you are aware, FDA published a proposed rule in December 2014 regarding electronic distribution of prescribing information. We have received your comments and we are in the process of finalizing the rule, but, at this time, FDA's expectation is that consignees will be provided with a hard copy of the *Circular*.

MODERATOR: Thank you, Wendy.

Background: FDA's August 2016 recommendations created a national policy for Zika virus ID-NAT testing for all blood donors in all states and without an option for testing of pooled samples.

Question 4: What criteria would be required by FDA before re-evaluating the policy of ID-NAT testing for every donor in every state?

NAKHASI: Obviously, there is a lot of uncertainty in the Zika epidemic, as we know. And I understand that there is a lot of anxiety about testing. So, at this point, the FDA's current thinking is that the FDA will continue to monitor the evolving Zika epidemic in the United States and its territories and will periodically evaluate the current policy. We may have some discussion at the Blood Product Advisory Committee meeting which is going to be happening November 18th even though it's just an informational session. There is no question/answer session. But I think at this point basically we are evaluating as the epidemic proceeds.

MODERATOR: Thank you, Hira.

MODERATOR:
Question 5: What options would FDA consider for a risk-based approach similar to the

testing scheme voluntarily implemented for West Nile virus testing; minipool testing with conversion to individual donor testing based on a trigger?

NAKHASI: An excellent question. But one has to understand there are differences in the transmission of Zika and West Nile virus. Zika epidemiology cannot be based exclusively by mosquito transmission. Unlike West Nile, Zika can be transmitted sexually. So, establishing a trigger to individual donor testing during periods of local mosquito borne transmission only would not be effective in reducing the risk of transfusion transmission of Zika.

Minipool testing in general, as you know, is less sensitive than the individual testing and we know from the data presented so far publicly that we miss certain individuals on the minipool NAT.

In addition, the medical consequences of Zika virus transmission must be considered. Particularly, the risk of pregnant women which can have serious implications on the development of the fetus.

The bottom line is that there are differences in the West Nile and Zika and one rule does not fit all.

Thank you.

MODERATOR: Thank you, Hira.

Background: FDA's December 2015 guidance*, Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products,* provides revised donor deferral recommendations for individuals with increased risk for transmitting HIV infection for use when revising donor educational materials, Donor History Questionnaires and accompanying materials, along with revisions to donor requalification and product management procedures.

Question 6: Without adding questions to the area for additional questions on the v2.0 DHQ, can we replace less restrictive questions with more restrictive questions and still consider this the AABB's v2.0 DHQ recognized by FDA? Or would we be required to submit our changes in a PAS for FDA approval?

And the follow up to that is:

Question 7: What criteria can we follow to determine what type of changes can be made to the v2.0 DHQ and documents without submitting a PAS?

MCBRIDE: Thank you, Sharon.

We are aware of unsolicited proposals to include more restrictive questioning in the accepted AABB DHQ version 2.0 and they are currently under consideration by the FDA. In accordance with the May 2016 FDA guidance for industry on implementing the DHQ v2.0 and the AABB DHQ User Brochure, if you elect to add a stricter question at the end of the questionnaire you may report this in your next annual report.

However, adding questions within the body of the FDA recognized v2.0 DHQ may impact a reporting category and consequently may require more extensive review. FDA's guidance recognizes these documents (the DHQ and accompanying materials as components of a system for establishing donor eligibility) as acceptable as submitted. Once revised by a blood center these documents may no longer be recognized by FDA if there are changes to the content, order or language other than the editions and reformatting described in the guidance. We therefore recommend you contact your consumer safety officer first to discuss the details of the changes on a case by case basis.

We have specifically received additional questions about whether the AABB DHQ v1.3 with the more restrictive MSM deferral within the body of the DHQ can still be used. Specifically, can the "from 1977 to the present time frame" in v1.3 still be used for MSM? As you are aware, DHQ v2.0 was updated to include FDA's most current policies and requirements. Some of the new requirements such as xenotransplantation are not included in v1.3. Therefore, we would prefer that you start using v2.0 and add a question at the end asking male donors if they have ever had sex with another male [if you are retaining the more conservative question MSM question].

You would also need to update the educational materials and add a flow chart. You may make this change and report it in your next annual report in accordance with the guidance.

To summarize add a question about MSM "ever" to the additional questions area of version 2.0 DHQ and report it in your next annual report, or for all other changes first contact your CSO and discuss how you propose to change the accepted DHQ. We will evaluate each request on a case by case basis and determine the reporting category.

MODERATOR: Thank you, Rick.

MCBRIDE: The follow up question, "**What criteria can we follow to determine what type of changes can be made to v2.0 DHQ and documents without submitting a PAS?"** The FDA guidance document, in recognizing the AABB version 2.0 DHQ, contains descriptions of the different types of modifications that can be reported in an annual report such as adding additional more restrictive donor selection criteria in the additional question area specific to your organization, displaying flow charts in another format compatible with your firm's current process, providing there's no change in the content other than stricter donor deferral criteria, and reformatting other DHQ documents to be consistent with your firm's current process provided neither the wording nor the order of the content in a DHQ is changed.

We state in the guidance that any other change must be reported as a PAS submission. However, again, we recommend contact your CSO, discuss the reporting category for a specific change that you feel is not addressed in the guidance and we'll go from there.

MODERATOR: Thank you.

Background: With regard to gender identity, the December 2015 HIV Risk Reduction Guidance states "In the context of the DHQ, FDA recommends that male or female gender be taken to be self-identified and self-reported." However, appropriate use of gender

identity is necessary for several reasons that are unrelated to evaluation of HIV risk, including protection of the donor's health and to ensure the quality of the product for the patient.

Question 8: What are FDA's specific recommendations, unrelated to HIV risk assessment, regarding evaluation of transgender donors to protect donor safety and product quality purposes?

Question 9: Should we use sex at birth, or as self-identified, when we enter donor information in the program used by apheresis machines to set up an appropriate collection procedure? [The operator's manual requires an entry for donor's sex to achieve an accurate calculation of TBV required to set up a collection procedure that ensures product quality (such as determining concentration and yield for platelet collections necessary for proper storage), and donor safety (such as limits on total volume collected etc)].

Question 10: Self-identified transgender males will not be assessed for history of pregnancy. How does the FDA suggest that these donors be assessed to assure both donor and recipient safety?

PAUL: Good afternoon, again. So, as Sharon stated, the FDA guidance issued in December 2015 contains our policy on gender identity and states that we accept self-identification of male or female gender. We did not specify how a blood establishment should address this issue for HIV or any other risk assessment. The medical director may exercise discretion where needed for issues concerning donor and product safety.

MODERATOR: Thank you, Wendy.

And now we're going to turn our attention to BECS.

Background: On March 1, 2016, FDA issued the proposed rule, Classification of Blood Establishment Computer Software and Accessories, proposing to classify the blood establishment computer software (BECS) and BECS accessories into class II (special controls).

Question 11: What would the proposed §864.9165 include as a BECS Accessory?

- **What are examples that would not be BECS accessories? For example, a barcode reader in the blood bank is part of the BECS. Is a barcode reader a BECS accessory when used at the patient bedside at the time of transfusion?**
- **Is software used to identify donors (based on donor data in the BECS) for use in donor recruitment purposes a BECS accessory?**

Question 12: What criteria can be used to understand the distinctions?

MERCADO: We received comments on the proposed rule, so we are aware of these issues. However, we will address the issues in the final rule.

MODERATOR: Thank you, Teresita.

ILLOH: As Teresita said we did publish a proposed rule concerning BECS and BECS accessories. We received really good comments concerning the proposed rule, including some of these questions. So we do intend to address these in the final rule. And, at this time, we're working on finalizing the rule, so there's not much that we can say at this time.

MODERATOR: Thank you, Orieji. Now we move to the questions regarding the March 2016 draft guidance on bacterial risk control strategies.

Background: Regarding the March 2016 draft guidance, *Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion,* once platelets are collected, the sequence of manufacturing activities varies widely based on who performs the activities (and when) for testing for bacterial contamination, pooling, storage, and distribution. The complex scheme addresses compliance with the new regulations of §606.145 and the varied path from collection to transfusion but it is difficult to understand.

Question 13: Is a transfusion service supposed to test for bacterial contamination before distribution of pooled platelets if the whole blood-derived platelets were sent to us by our supplier as "tested negative for bacterial contamination," stored and then pooled in our blood bank? What circumstances require the transfusion service to test rather than the supplier?

HADDAD: I'll take these questions.

On the topic of bacterial contamination of platelets and, as many of you already know, the new regulation went into effect on May 23rd, 2016, and that's regulation §606.145. And it states that blood collection establishments and transfusion services must assure that the risk of bacterial contamination of platelets is adequately controlled using FDA approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose by FDA.

So, one element of this question is this regulation. Another element is the FDA draft guidance that was issued for public comments in March of this year and entitled, "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion." So, what we are stating at this point is that after the implementation of §606.145 back in May of this year and pending the implementation of the aforementioned guidance once it is finalized we have determined that the requirements of §606.145 can be met by one of two ways, either by testing for bacterial contamination at least once the platelet collection or the transfusable platelet product with an FDA cleared device according to its instruction for use, or by pathogen reducing the platelet collection using an FDA approved pathogen reduction device according to its instruction for use.

And what I have just stated is in the draft guidance on page 7. In other words, to currently satisfy the regulation, the product needs to be tested at least once, either at the collection center or in the transfusion service.

So, in the specific scenario that was described in the question we have single units of four whole blood-derived platelets that have tested negative for bacterial contamination and the transfusion

service is making a pool out of these single units. In this case, the units have all been tested at the collection center and the pool made out of these units need not be retested to satisfy the regulation at this time.

And there's a corollary question that you have mentioned, what circumstances require the transfusion service to test rather than the supplier?

As I have indicated if the supplier does not test the product then the transfusion service has to. If the single units were not tested at the collection site then the pool would need to be tested by the transfusion service.

MODERATOR: Thank you.

Question 14: How does the scheme differ for pooled platelets and apheresis collections?

HADDAD: I'm going to refer the audience to the draft guidance I mentioned earlier as it describes our current considerations on testing pooled platelets and apheresis platelets.However, this is only a draft guidance. It has been issued for comments purposes only. Currently, we are reviewing the public comments to the draft guidance and we will finalize our recommendation at the conclusion of the review process.

MODERATOR: Thank you.

Question 15: Please describe acceptable processes to extend the platelet expiration to 7 days? What are the critical steps (or goals of the process) that FDA considers necessary to create a 7-day product?

HADDAD: My answer is partly similar to that of question 14. The draft guidance has our current considerations on the extension of platelet shelf life to seven days. The final guidance will include our comprehensive recommendations on this issue, again after review of the public comments.

However, I would like to point out that seven-day platelets can be available now and they need not wait the finalization of the guidance. To make seven-day platelets you need two elements and they are both currently available in the U.S. First, you need to collect and store platelets in properly labeled seven day bags, meaning that the bags should be labeled with a requirement that the platelets get tested with a safety measure bacterial detection test.

And second, of course, you need to test the platelets with the safety measure test.

When the properly labeled bag and the safety measure test are used jointly, according to their instruction for use, the shelf life of the platelets can be extended to seven days. Establishments interested in implementing seven day shelf life need to register with FDA.

MODERATOR: Thank you, Salim.

Question 16: What is FDA's timeline to provide a final platelet guidance to address reduction of bacterial contamination?

HADDAD: Traditionally in the month of January of every year we post on our website a list of guidance documents with their expected publication dates. We encourage you to go to our website in January and review the list of guidances that would be published.

MODERATOR: And I think that might apply to Question 17 that says,

Question 17: When will FDA provide a simple pathway to manufacture and licensure of pathogen inactivated triple collection platelet products?

HADDAD: Well, it is correct that pathogen reduced triple collection of platelets are currently not available in the U.S. In terms of when might they become available we do not traditionally comment on what is or what is not in the FDA regulatory pipeline.

However, interested parties would need to contact the manufacturers of pathogen reduction devices directly with this question.

MODERATOR: Thank you, Salim.

And now we're going to turn our attention to questions related to CLIA regulations and, specifically staff competency.

Background: 42 CFR 493.1451(b)(8) provides the requirements for evaluating competency of staff performing high complexity testing.

18. Several questions were submitted:

- **Does my lab need to use all of the criteria for evaluating staff competency (direct observation, result reporting, record review, proficiency testing, instrument maintenance, problem solving etc) for each individual test we perform? Or can we group like tests together and use different competency evaluation methods for each as shown in the example below?**

Example: ABORh- do a direct observation, and review testing results, and perform a proficiency test, and perform centrifuge maintenance, and perform reagent QC…

vs.

Antibody identification- use direct observation for a primary LISS panel; use monitoring, recording & reporting results for an eluate use a proficiency test for antigen typing…

- **What about staff competence regarding tasks that are not considered testing and don't really fall into the pre-analytic, analytic, post analytic system such as issuing blood products, washing red cells, pooling cryoprecipitate?**

Penny is prepared to answer these questions…

MEYERS: Good afternoon. Before I give my first answer I'll give my usual disclaimer which is that the answers that I'm providing today pertain specifically to the CLIA regulations.

However, if your laboratory obtains its CLIA certification by virtue of accreditation by a CMS-approved accreditation organization, then your laboratory must follow all of your accreditor's requirements which may be more stringent than CLIA. Okay. Now back to the question.

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

MODERATOR: And our next related question is: "**What about staff competence regarding tasks that are not considered testing and don't really fall into pre-analytic -- analytic post-analytic systems such as issuing blood products, washing red cells, pooling cryoprecipitate"**?

MEYERS: CLIA requirements for competency evaluation apply to laboratory testing that is subject to CLIA regulation. Activity such as issuing blood products, washing red cells and pooling cryoprecipitate are blood manufacturing activities that are not subject to CLIA.

Thus, competency evaluation is not required by CLIA although it may be required by other regulatory or accreditation agencies.

MODERATOR: Thank you, Penny.

Background: The requirement for competency assessment, to include assessment of test performance by testing previously analyzed specimens, internal blind testing samples or external proficiency testing samples, is provided in 42 CFR 493.1451(b)(8)(v).

Question 19. Can CMS/CLIA clarify what is needed for "Competency Assessment of test performance through testing - Previously analyzed specimens, or- Internal blind testing samples, or- External proficiency testing samples" in the case of automated analyzers when external PT/internal blind samples are unavailable for every technologist?

MEYERS: Laboratories have the choice of the three types of samples listed in the regulation. They don't necessarily have to use all three types. The wording says "or." So laboratories are not required to use internal blind testing samples or external proficiency testing samples if they're not available. Previously analyzed specimens will also fulfill the requirement.

MODERATOR: Thank you.

Background: Under §§493.1256(e)(4)(i) and 493.1256(e)(4)(ii) Standard: Control procedures, regulations and interpretive guidelines previously allowed quality control of certain types of culture media following the National Committee for Clinical Laboratory Standards (NCCLS). The revised regulations, effective January 1, 2016, do not recognize the NCCLS and has a significant impact industry wide. Blood centers use culture based methods, such as the BacT/ALERT BPA culture bottles using the BacT/ALERT® 3D System to test platelet products as an in-process qualitative sterility test for determining

the presence or absence of potential contaminating bacteria. It is not used for reporting results for patient diagnostic purposes or for identifying microorganisms. Samples with culture results flagged as positive by the equipment are referred to an external CLIA certified clinical reference laboratory for isolate identification testing.

The questions are:

Question 20 (a): First, what was the rationale for not allowing use of the NCCLS standards for QC of certain types of media?

- **And second what is the basis for applying §§493.1256 (e)(4)(i) and 493.1256 (e)(4)(ii) QC requirements to in-process sterility based qualitative testing method such as BacT/ALERT testing?**

MEYERS: The CLSI, formerly NCCLS or NCCLS material, that was previously contained in the CLIA interpretive guidelines and that were allowed to be used in lieu of following the regulations, is copyrighted material and we are no longer able to use it.

However, the interpretative guidelines now contain a different alternative quality control option called Individualized Quality Control Plan or IQCP. IQCP can be used by laboratories in lieu of following certain CLIA QC regulations. IQCP requires a risk assessment, a quality control plan and quality assessment activities.

Laboratories can use the data that they have collected over the years while using the CLSI guidelines as part of their risk assessment. As a result of the risk assessment, they may find that the QC that they have been doing all along is sufficient, or they may find additional sources of error that need to be addressed.

Additional information about IQCP can be found in the interpretative guidelines on the CLIA website.

MODERATOR: And the related question,

Question 20 (b): And second what is the basis for applying §§493.1256 (e)(4)(i) and 493.1256 (e)(4)(ii) QC requirements to in-process sterility based qualitative testing method such as BacT/ALERT testing?

MEYERS: We believe that this questioner is really asking why does any CLIA regulation apply to testing for bacterial contamination. In order to determine whether the testing is subject to CLIA regulation, it is helpful to examine the CLIA definition of a laboratory and that's what we have to go back to. The regulation at 42 CFR Part 493.2 defines a laboratory as a "facility for the biological, microbiological. . . or other examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention or treatment of any disease or impairment, or the assessment of health of human beings. These examinations also include procedures to determine, measure or otherwise describe the presence or absence of various substances or organisms in the body . . ."

While testing to detect bacterial contamination and platelet components is performed for the primary purpose of excluding unsuitable products from transfusion, it is our understanding based on AABB guidance to its membership that the results of this testing are also used for donor health purposes.

AABB Association Bulletin 05-02 advises, and I'm quoting here, "Donor notification is indicated for any suspected bacteramia with a possible pathogenic organism." The bulletin goes on to advise that the donor should be counseled about the potential medical significance of the results and advised to see a physician. Upon request of the donor, the results are provided to the physician.

The bulletin also advises that -- and I'm quoting again -- "notification of donors with an identified gram negative organism should be considered even before obtaining a confirmatory culture result because gram negative organisms generally indicate the presence of bacteremia."

So, in conclusion, because the results of bacterial contamination testing may be communicated to blood donors and used for the assessment of health or diagnosis of disease, it is the opinion of CMS that the testing is subject to all applicable CLIA regulations including those that were mentioned in the question.

MODERATOR: Thank you, Penny.

And now we have questions for CLIA as they relate to HCT/Ps so I'll ask Brandon to take over.

SANDINE: Thank you, everyone, for your time and your attention.

Background: CLIA regulations cover laboratory testing that is used to "treat" patients. CD34 and CD3 testing is performed by flow cytometry to calculate the dose of products administered to patients as part of a hematopoietic stem cell transplant or donor lymphocyte infusion.

Question 21: Could you please clarify whether these tests fall under CLIA regulations and why or why not?

MEYERS: These tests do not fall under CLIA regulations. CD34 and CD3 testing of hematopoietic stem cells or lymphocyte products is considered to be purity and potency testing of a product. It does not fall under the definition of a laboratory in CLIA that we talked about earlier. Such testing is part of the product manufacturing process which is under the purview of FDA. Survey and certification letter 11-O8-CLIA that addresses this topic can be found on the CMS website.

SANDINE: Thank you.

Background: Subsection F of the September 2016 guidance, Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Living Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), briefly discusses the availability of licensed NAT assays for use in testing living and cadaveric (non-heart-beating) HCT/P donors.

Question 22: Is there any mechanism by which pooled samples from HPC, Apheresis, bone marrow, and cord blood donors could be pooled? We outsource the testing of these products to our blood center which tests them along with blood donors in batches.

KARANDISH: I'll take that question.

Establishments must follow the manufacturer's instructions for use when testing a donor specimen for a relevant communicable disease. The instructions for use are carefully written based on supporting data that is submitted by the manufacturer and reviewed by FDA.

Currently, the instructions for use for the two available West Nile virus NAT test indicate pooling of samples is only intended for volunteer donors of whole blood and blood components.

For other living donors, which includes donors of HPCs and cadaveric donors, individual donor samples must be used with the available West Nile virus NAT test.

SANDINE: Thank you.

Background: In March 2016, FDA issued *Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products*. Subsequently, when the August 2016 guidance, *Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components,* recommended the immediate cessation of blood collection activities or IND testing for Zika virus (ZIKV) on all blood products in ZIKV active areas, HCT/P establishments grew concerned that such expedient recommendations would be placed on them. Currently, only one manufacturer's test, under IND, includes the testing of other living donors.

Question 23/24: Does FDA plan to require investigational testing for Zika virus for 351 and 361 HCT/Ps?

KARANDISH: FDA's current recommendations for screening all HCT/P donors for evidence of Zika virus are those that are described in the March 2016 guidance "Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, tTissues and Cellular and Tissue-Based Products, or HCT/Ps." At this time the guidance does not provide any recommendations for testing HCT/P donors for evidence of Zika virus.

FDA continues to work closely with U.S. government partners and manufacturers that are interested in developing tests for HCT/P donors and will consider appropriate recommendations for use of such tests as they become available. FDA recommendations will be communicated through guidance documents.

SANDINE:

Question 25: If a donor sample of an HCT/P is tested with the IND test for ZIKV how would the product be labeled?

Question 26: For an HCT/P that is intended to be imported from a ZIKV active area into the U.S. and, therefore an ineligible donor, what labeling and importation requirements

must be met? Additionally, what labeling requirements would apply if the donor had tested negative with the IND test method?

KARANDISH: If Zika virus testing is performed you must consider the results of the test when making a donor eligibility determination. In other words, a positive test result must be considered a risk factor for Zika virus infection even if no other risk factors were identified in donor screening. However, any negative or non-reactive test results would not override any risk factors identified in donor screening in accordance with the March 2016 guidance.

The 1271 regulations permit use of HCT/Ps from an ineligible donor in certain situations. For example, if there is an urgent medical need. If you use an HCT/P from an ineligible donor, then the labeling described under §1271.65(b) must be followed.

As another example, if a donor had a negative test result for Zika virus but recently traveled to an area of active Zika transmission, then the donor would still be considered ineligible and the HCT/P must be labeled as described in §1271.65(b).

I also have to mention that for use of available investigational blood donor screening tests for Zika virus it would be the responsibility of the establishment to contact the IND sponsor for using such tests for testing HCT/P donors.

SANDINE: Do you believe you've answered 26 as well?

KARANDISH: I think there is one part of 26 about import requirements for HCT/Ps that are described in §1271.420 so you can refer to that provision for those requirements.

SANDINE:

Question 27: For umbilical cord tissue that is stored and will subsequently be used as a source of stromal cells would any of the processing methods used for cryopreservation be defined as more than minimal manipulation?

KARANDISH: For an HCT/P to be regulated solely under Section 361 of the Public Health Service Act, the HCT/P has to meet the four criteria described in the §1271 regulations. Minimal manipulation is one of the defined criteria.

As you may know, FDA has published a draft guidance that describes the agency's current thinking about the interpretation of the minimal manipulation criterion. This past September FDA held a two-day public hearing to get input from stakeholders on the minimal manipulation and three other draft guidance documents related to the HCT/P regulatory framework. The comments that were submitted to the agency are under consideration.

To answer questions of this nature additional information would be needed. So, the inquirer may submit a request for recommendation to the Tissue Reference Group and the e-mail address is tissuereferencegroup@fda.hhs.gov.

SANDINE: Thank you.

Question 28: Our orthopedists often collect and inject autologous platelet rich plasma (PRP) as part of other orthopedic surgeries or procedures. What regulations would apply to them and under what conditions would the procedure fall into regulation as an HCT/P, if any?

KARANDISH: PRP described in this question does not meet the definition of an HCT/P. The inquirer can contact the CBER product jurisdiction officer for additional information. And the e-mail address is cberproductjurisdiction@fda.hhs.gov .

SANDINE: Thank you.

Background: Regarding the FDA requirement for facility registration, we are seeking clarification regarding when we should register with FDA separately or as part of our overall facility registration. Our transfusion service is registered.

We received two questions:

Question 29 (a): First, our cell processing laboratory is under a different leadership and quality unit (Oncology) than the clinical laboratory. Should we hold our own separate registration?

KARANDISH: Establishments that manufacture HCT/Ps are required to register and list their HCT/Ps with FDA in accordance with the §1271 regulations. It may be helpful to first review the definition for an establishment in the regulation.

Specifically, under §1271.3(b) establishment is defined as a place of business under one management at one general physical location that engages in the manufacturer of HCT/Ps.

What is meant by one general physical location? In 2007, FDA published a guidance titled, "Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Small Entity Compliance Guide." This guidance explains that each physical location will generally have only one registration for any combination of HCT/P types and/or functions unless the individual establishments are under different corporate entities. The guidance goes on to explain that one general physical location could be reasonably construed to include separate buildings within close proximity capable of being inspected at the same time.

Going back to the question, the cell processing laboratory appears to be involved in manufacturing HCT/Ps. Most likely they are processing peripheral blood stem cells or cord blood products. Therefore, the cell processing lab must register following the FDA's procedure for HCT/P registration.

SANDINE: Thank you.

Question 29 (b): Secondly, the microbial testing of our products is performed by our microbiology laboratory for 361 products, does the microbiology lab need to register with FDA for this manufacturing step?

KARANDISH: In the §1271 regulations the definition for processing include microbial testing. If the cell processing lab is registered for processing HCT/Ps then we would not expect the microbiology lab to submit a separate registration.

The microbiology lab and the cell processing lab described in this scenario are considered to be in one general physical location and under the management of the same corporate entity, even though the daily operations may be managed by different groups.

SANDINE: Thank you.

Background: §1271.220 (b) *Pooling.* Human cells or tissue from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.

30. Questions:

- **Can you clarify the intent of 21 CFR 1271.220(b) as it applies to monozygotic (identical twins with 1 placenta) twins for cord blood collection?**
- **Specifically, what concerns are present that preclude the pooling of cord blood from monozygotic twins?**

KARANDISH: In this scenario, and actually I think I'm going to answer the second part of the question, too. In this scenario each baby is a donor and cord blood is being collected for each donor. Combining or pooling collected cord blood from two donors could introduce contamination or cause cross-contamination.

FDA recognizes that there may be situations when pooling may be necessary and the benefit of pooling may outweigh the risks. In those cases, you may request an exemption or alternative under §1271.155.

SANDINE: Thank you. I'll pass the mic to Sharon again.

MODERATOR: Thank you, Safa and Brandon.

Our next topic area is plasma and weighing donors, and references FDA's memorandum dated 11/4/92, "Volume Limits for Automated Collection of Source Plasma."

Background: The FDA Memorandum, *Volume Limits for Automated Collection of Source Plasma*, dated 11/4/92, provides the following regarding plasma collection volume limits:

> **To promote rapid implementation of such simplified schema, the Center for Biologics Evaluation and Research is informing all manufacturers that the following limits may be adopted without further notice. The anticoagulant volume is included in the third column below. This volume is based on a 1:16 (0.06) ratio of anticoagulant to anticoagulated-blood.**

Donor Weight	Plasma Volume	or	Weight Collection Volume
10-149 lbs	625 mL (640 g)		690 mL (705 g)
150-174 lbs	750 mL (770 g)		825 mL (845 g)
175 lbs & up	800 mL (820 g)		880 mL (900 g)

Question 31. Our blood center only collects 600 ml's of plasma. Based on FDA's memorandum dated 11/4/92, any donor up to 149 lbs. can donate 625mLs. If our blood center limits plasma collection to the minimum weights allowable, are we required to weigh the donor? If so, why?

MCBRIDE: Thank you. The first part of the question, short answer, yes. You are required to weigh - in accordance with 21 CFR 630.15(b)(3) which states that the establishments that collect plasma by plasmapheresis must weigh the donor at each donation.

Why? The rationale is described in the preamble to the donor eligibility final rule on page 29873. It's in the Federal Register, Volume 80, issued May 22nd, 2015.

In short it states, a current weight measurement permits the collecting establishment to calculate accurately the plasma volumes to be collected based on a weight specific nomagram which is described in the 1992 memorandum.

The need for accurate measurement applies to all collections by plasmapheresis whether Source Plasma or frequent or infrequent plasmapheresis collection. When there is a co-collection, including plasma by apheresis, this provision requires the establishment to weigh the donor because a collection of plasma by apheresis will still be based on the donor's weight in the nomogram.

So weighing a donor is required regardless of the type of plasma product collected, amount of plasma collected during apheresis, frequency of the plasma collection, intended use of the plasma whether for transfusion or further manufacture, and whether the plasma is collected as a stand-alone, sole product or as a co-component with a platelet or RBC apheresis collection.

We just ask that you make sure the "hold" buttons on the scales are not engaged.

We have not included a requirement to weigh plateletpheresis donors. However, we have gotten a few questions about PAS platelet collections (platelet added solution) collections and weighing the donors.

We consider the collection of PAS platelets to be a plateletpheresis procedure. In other words, you only collect the PAS platelets during the plateletpheresis procedure. You prepare a plasma product from the platelets so it is not considered a plasmapheresis collection procedure and, therefore, the donor is not required to be weighed.

However, if you do co-collect a separate plasma product during the PAS plateletpheresis procedure then the donor must be weighed.

Thank you.

MODERATOR: Thank you, Rick.

Background: When AABB and FDA participants met in an executive-level liaison meeting in May 2016, one topic of discussion was the regulatory pathway under development by the

FDA that will provide options, other than labeled Recovered Plasma, for plasma to be sent to fractionators for further manufacture. At that time, with regard to plasma collected by apheresis, FDA participants noted that the pathway to be outlined in a draft guidance will reconcile with the CFR requirements regarding the intent for use of the product at the time of collection: transfusion vs. further manufacturing.

Question 32: What is the status of allowing the conversion of apheresis plasma to Recovered Plasma prior to expiration and providing flexible options, in addition to Recovered Plasma, for plasma shipped to fractionators for further manufacture?

ILLOH: So, I'll take this one.

You're correct. We did meet to discuss this topic and we are aware of ongoing discussions and concerns regarding the need for a pathway for collection of plasma for further manufacture and inventory flexibility and blood collection centers.

This issue continues to remain a priority for us and we're looking at this issue. In fact, we've announced publicly in the guidance agenda that we intend to publish guidance related to this issue.

Now, as we look at this issue, there are some questions that we're trying to resolve. As you know, Source Plasma and Recovered Plasma are the plasma products that are currently used for further manufacture in the U.S. So, FDA must consider the existing regulations for these products as we attempt to define and establish standards for new plasma products for further manufacture.

We've encountered a significant hurdle for what we're calling Concurrent Plasma. Putting this new product in a guidance document is a potential conflict with our current regulations and definition of Source Plasma which we can find at 21 CFR 640.60. Under these regulations, plasma collected by plasmapheresis for further manufacturing use is Source Plasma and regardless of whether the plasma is collected concurrently or collected alone. So, that's really the issue we're running into.

Therefore, short of a change of the regulations, plasma collected concurrently with a single component and labeled for further manufacture must meet the applicable product standards for Source Plasma. Now we recognize that this is a problem because one of the standards is the requirement for immediate freezing which cannot typically be done with mobile collections. This may not be feasible for most blood collection establishments because of these limitations.

We're continuing to consider the options available through guidance and regulation, and our goal is to ensure that the ultimate pathway is one that meets the needs of our industry, maximizes each donation and reduces wastage of plasma.

So, bottom line, we are looking at guidance. We've encountered some issues that we need to resolve with guidance, and we might also have to look at rulemaking to resolve this.

MODERATOR: Thank you, Orieji

Our next three questions relate to labeling based on historical antigen typing records. Use of historical donor antigen typing records can expedite the identification of safe blood products for the recipient.

Background: Antigen typing is performed to identify donor antigens when addressing the special transfusion needs of the recipient. Use of historical donor antigen typing records can expedite the identification of safe blood products for the recipient.

Question 33/34: Can RBCs be labeled with the antigen typing results from historical records? If so, are there any specific requirements, for example, serological versus genotyping performed on one -- on more than one day or sample, et cetera?

Question 35: If not, when does CBER plan to issue recommendations regarding the use of historical RBC antigen typing to label blood products?

PAUL: This topic was discussed at a Blood Product Advisory Committee in December 2012. The committee heard presentations that described the current practices in the United States as well as Canada and also some suggestions from the AABB work group. At this time, it is our current consideration to put this on the Regulatory Agenda and to issue a draft guidance document.

All of the issues will be addressed in the guidance document and we look forward to receiving all of the public comments on that draft guidance.

MODERATOR: Thank you, Wendy.

Question 36: The May 2015 Final Rule included new requirements for Medical Directors that places limits on delegation of authority for some activities.

- **Can the Medical Director of a Transfusion Service delegate, in writing, the review of market withdrawals for non-infectious disease testing to a member of the QA unit?**
- **Is the Medical Director required to review and sign ALL market withdrawals?**

ROGERSON: Thank you for the questions.

The revised regulations define and reference a responsible physician in the context of donor eligibility and in the context of collection of blood and blood products. They do not specifically address the position or responsibilities of the medical director regarding market withdrawals.

For regulations regarding market withdrawals and recalls, please refer to subpart C of 21 CFR Part 7, beginning at §7.40.

Additionally, on FDA's website there is guidance for industry, "Product Recalls, Including Corrections and Removals."

MODERATOR: Thank you.

Background: New minimum requirements in FDA's May 2015 final rule lowered hemoglobin and hematocrit requirements based on the normal range for female donors.

New regulations at §630.10(f)(3)(i)(A) authorize blood collection "from female allogeneic donors who have a hemoglobin level between 12.0 and 12.5 grams per deciliter of blood, or a hematocrit value between 36 and 38 percent, provided that you [the establishment] have taken additional steps to assure that this alternative standard is adequate to ensure that the health of the donor will not be adversely affected due to the donation, in accordance with a procedure that has been found acceptable for this purpose by FDA."

Question 37: I have read a lot about the donor safety concerns related to collecting Whole Blood from a female with a hemoglobin between 12.0-12.5g/dL. My question relates to the transfusion recipient: by providing an RBC or WB unit with this lower hemoglobin, are we providing an optimal product for the transfusion recipient when compared to a collection from a male donor with a hemoglobin greater than 13.0g/dL?

ILLOH: I'll take this one. This is a great question and the answer is, yes. We believe so.

Our revision to the hemoglobin standards to allow donations from female donors with hemoglobin levels between 12 and 12.5 grams per dL or hematocrit values between 36 and 38 percent included considerations for donor safety and product potency. We did look at those two issues.

In fact, in the preamble to the final rule, if you look at that, I'll state what we quoted there: "We have determined that standard collections from donor -- from a donor with a hemoglobin level as low as 12.0 grams per deciliter of blood or the hematocrit value of 36 percent would meet minimum potency levels based on calculated hemoglobin content."

Now, we are all aware that, in this country, we don't really have a standard of hemoglobin content for our units. But what we did was to estimate the hemoglobin content to standard units that would be collected from female donors with these hemoglobin levels and we determined that the hemoglobin content of such units would meet internationally recognized standards for hemoglobin content and that also the product specifications provided in some apheresis are received devices. We're confident that these units would meet the product potency standards.

MODERATOR: Thank you, Orieji.

Background: In the May 2015 Final Rule, the requirement to evaluate donors for a history of viral hepatitis after the age of 11 was removed. "Instead under new §610.3(h)(1)(iii) an establishment must defer a donor exhibiting signs and/or symptoms of relevant transfusion-transmitted infection, including HBV and HCV." Reactive test results for these relevant transfusion-transmitted infections would result in donor deferral as described in §610.41(a).

Question 38: The donor center has no testing history on file for the donor. He is 48 years old and has hereditary hemochromatosis with a valid prescription order from his physician. He has always been treated as a therapeutic phlebotomy with discard because at his first donation he gave a history of hepatitis B at age 18. He is currently feeling healthy and well, shows no signs or symptoms of hepatitis and is not under a physician's care for

hepatitis. He meets all other criteria for donation. Is this donor now eligible to donate as an allogeneic donor?

EDER: So, I'm going to make a few general comments and then speak to the scenario.

The long-standing requirement to question donors about a history of viral hepatitis was introduced in the late 1950s, before specific laboratory tests were available for hepatitis B and hepatitis C, and persisted when it was unknown if there were other chronic hepatitis viruses that could be transfusion transmitted.

In the 2016 final donor eligibility rule, the rule does not refer to a history of viral hepatitis after age 11 as a factor in determining donor eligibility. But to be eligible a donor must be in good health and free from transfusion-transmitted infections under §630.10(a). The donor is not eligible to donate if the purpose of donating is to obtain test results for a relevant transfusion-transmitted disease under §630.10(e)(2). And reactive test results for relevant transfusion transmitted infections such as hepatitis B and hepatitis C would result in donor deferral as described in §610.41(a).

As a general matter, FDA has not provided recommendations for an acceptable requalification method for donors who had provided a history of hepatitis after age 11, under §630.35(b). Therefore, such donors would remain deferred until re-qualified by a method or process found acceptable by FDA. FDA may consider developing guidance about requalification under §630.35(b) for a donor previously deferred because of a history of viral hepatitis.

So, now for the scenario. This donor would have been indefinitely deferred at his first donation for reporting a history of hepatitis B. If the donor did, in fact, have hepatitis B at age 18, he would likely remain anti-hepatitis B core antibody positive which persists for life after infection and he would remain deferred under 21 CFR 610.41(a).

So, no, he is not eligible.

MODERATOR: Thank you.

Question 39: A husband and wife both present for donation. Neither have ever donated at the center. Both are feeling healthy and well on the day of donation. The husband is screened first, meets the eligibility criteria and begins his donation. His wife is then screened and answers "Yes" to the question "In the past 12 months have you had sexual contact with a person who has hepatitis?" She gives the information that her husband had hepatitis B 10 years ago but is currently not under a physician's care and has no signs or symptoms. Is the wife eligible to donate (if she meets all other eligibility requirements) and if not, does her husband's donation need to be quarantined and discarded?

EDER: Consistent with the donor history questionnaire, the wife would be deferred for 12 months for having sexual contact with a person with hepatitis B. The question about sexual contact does not distinguish if it's asymptomatic or symptomatic. And the scenario raises the possibility that she would be deferred for 12 months.

The situation now identifies reliable third party information about the husband. It happens, for which blood centers should have a procedure to manage and investigate further. So, your medical director should evaluate such situations and make the final determination of donor eligibility. However, FDA's current consideration is that it would be prudent to quarantine and discard the donation and defer the donor under investigation.

MODERATOR: Thank you.

Question 40: Is it possible to have recovered from hepatitis B? Can a donor have "had" hepatitis as opposed to "has" hepatitis? If a donor was deferred in the past for hepatitis after the age of 11 but does not recall what type of hepatitis they were diagnosed with are they now eligible to donate?

EDER: Yes, hepatitis B infections can resolve. Donors who had previously reported a history of hepatitis after age 11 would have been indefinitely deferred. As in the first case if a donor did, in fact, have a history of hepatitis B he would likely remain anti-hepatitis B core antibody positive which persists and would be deferred under 21 CFR 610.41(a).

For the last part of this question, the unknown type of hepatitis, 21 CFR 630.35(b) requires that donors deferred for reasons other than under §610.41(a); that is, reactive test results, for relevant TTIs, you determine that the donor has met criteria for requalification by a method or process found acceptable for such purpose by the FDA.

At this time, the FDA has not provided recommendations for requalification of donors with a history of hepatitis under §630.35(b). You may consider the following options in this scenario:

- Individual donor re-entry requests sent to FDA on a case by case basis;
- FDA licensed blood establishments can submit their SOP as a PAS submission describing their requalification method;

FDA must find a requalification method proposed by an unlicensed establishment to be acceptable before its implemented.

MODERATOR: Thank you, Anne. And now we're going to shift to Chagas and HTLV infectious disease testing.

Background: FDA recommendations in the December 2010 *T. cruzi* guidance concurred with the industry practice of one-time testing of each donor for antibodies to *T. cruzi* which began on a voluntary basis in 2007. Currently, blood donors who test repeatedly reactive on a licensed screening assay are indefinitely deferred from donation. BPAC members concluded that a reentry algorithm is needed based on discussions at the July 2014 meeting.

A similar scenario exists for donor deferral based on HTLV-I/II testing, and the need for re-entry options for indefinitely deferred donors as discussed at the November 2011 BPAC meeting.

Question 41: With licensed supplemental tests now available for Chagas and HTLV-I/II, is FDA considering recommendations for re-entry that would have a positive impact on the

number of donors eligible to return and the resulting improvement for a safe and adequate blood inventory?

EDER: Yes. FDA is considering recommending a reentry algorithm for donors who test reactive on a screening assay for antibodies to *T. cruzi*. CBER has announced its intention to issue draft guidance that would amend the 2010 *T. cruzi* guidance on the 2016 Guidance Agenda that is posted on the CBER website in January.

For HTLV reentry, the Blood Products Advisory Committee discussed the issue in November 2013. Considering the recommendations of the committee, FDA requested additional data from the sponsors to demonstrate that donors with repeatedly reactive results on an HTLV antibody screening test, but only limited reactivity on the HTLV-I/II blot with a single gag band or multiple gag bands without p24 are not infected.

The data collected for so far is not conclusive. However, given the difficulty in getting sufficient data, FDA is willing to take the matter under reconsideration and address alternative algorithms.

Please note that 21 CFR 610.40(e) requires further testing of each donation found to be reactive using the licensed supplemental test. Therefore, effective -- well, it became effective May 2016, blood establishments must further test such donations using the licensed supplemental test for *T. cruzi* and HTLV to provide additional information to the donor regarding his or her infection status.

MODERATOR: Thank you, Anne.

Background: FDA's use of an exception, available under new §640.120(b), that permitted CBER to designate Zika virus as a new RTTI has led to speculation on FDA's future plans for *Babesia* testing requirements.

Question 42: Does FDA plan to issue a guidance document to address *Babesia* and should we expect *Babesia* testing requirements in the near future?

NAKHASI: Boy, how the times have changed. A few years back *Babesia* was top, first few questions and now it's the last question on this session! Kidding aside, FDA discussed, as you know, strategies for implementation of serological and nucleic acid testing for *Babesia* in blood donors with the Blood Product Advisory Committee in May 2015.

FDA is currently considering issuing a guidance document to address *Babesia* should a licensed test become available. This guidance will take into consideration the recommendations provided by the BPAC. I know there is a lot of anxiety because Zika was out there, before the Zika guidance came out, before the tests are available.

But let me reiterate that the [*Babesia*] guidance will come only once the licensed test becomes available. Thank you.

MODERATOR: Thank you, Hira.

I want to thank everyone who submitted questions to this session in support of it. We really appreciate that. And if you have more questions, please contact your consumer safety officer at the FDA for assistance.

I want to thank all of our speakers for the time and effort they put in to support this session. Thank you very much.