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PERSPECTIVES ON IN VITRO DIAGNOSTIC DEVICES,
REGULATED BY THE OFFICE OF BLOOD RESEARCH AND REVIEW

FOOD AND DRUG ADMINISTRATION
WHITE OAK CAMPUS
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TUESDAY, JULY 16, 2019
8:30 A.M.

APPEARANCES:
MODERATORS: Julia Lathrop, PhD, DETTD/OBRR
J. Peyton Hobson, PhD DETTD/OBRR

WELCOME:
JULIA LATHROP, PHD, DETTD/OBRR

INTRODUCTION:
Nicole Verdun, MD, OBRR

PRESENTERS:

Anne Eder, MD, PhD, OBRR

Iwona Fijalkowska, PhD, DETTD/OBRR

Caren Chancey, PhD, DETTD/OBRR

Rana Nagarkatti, PhD, DETTD/OBRR

Lori Peters, MS, DMPQ/OCBQ

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CONFERENCE

MONDAY, JULY 15, 2019

8:00 A.M.

DR. LATHROP: Good morning. I'm Julia Lathrop, the Associate Deputy Director in the Division of Emerging and Transfusion Transmitted diseases, and I'll be moderating this first session. Before we get started, I'd like to touch on some housekeeping.

Everybody should have gotten a little card that has the wi-fi. The network is FDApublic and the password is publicaccess. The restrooms are located, if you go towards the big screens and turn right, they're down the end of that hall.

There's also vending machines down there, but don't forget to preorder lunch if you want to get lunch from the kiosk, because it gets pretty crowded if you don't preorder. The panel will handle questions if there's time at the end of each presentation, we'll have some Q and A.

But there are also Q and A sessions scattered throughout the day, so that will give you the opportunity to ask questions then. Also we will be monitoring the web for people on the web. You can type in your question and we will read them out during the Q and A sessions. So please feel free and ask questions that way.

For the DETTD Q and A, people who have signed up come to the registration desk at 2:30, the break between the general and the DETTD specific session, and we'll give you a card that will tell you what room to come to and what time to show up. So, for the one on one, okay?

So Nicole Verdun, the Director of the Office of Blood Research and Review, will start things off. Nicole.

DR. VERDUN: Okay, so I just wanted to take this time to welcome all of you and thank you for being here. We are very, very happy to see everyone here and also everyone that's actually participating on the web. So today's workshop is going to be perspectives on IVEs regulated by the Office of Blood Research and Review.

So really the goals of this workshop today are for you to understand FDA's approach and thinking to the review of submissions regulated in OBRR. And this is really an opportunity, this is meant to be interactive. And so if you have any specific questions, please

feel free to ask them.

In addition, we will be highlighting throughout the day and tomorrow common issues that are experienced and helpful hints to improve the review experience for both sponsors and FDA. In addition, this is meant to really enhance communication between industry and FDA, so likewise we would like to hear from you if there are specific things that you would like to let us know about.

And lastly, I would like to just start the workshop by acknowledging all of the hard work that went into putting this workshop together. Specifically, we had a workshop working group that worked tirelessly over these past several months to make this happen.

In addition, we have several people within our office and also within offices that we work quite closely with that have helped to make this happen. In addition, our Office of Communications, which is, you will see also throughout the day today, has helped in putting this workshop together.

So without any further ado, I want to welcome you and we will get started and we are very excited to have all of you here. Thank you.

DR. LATHROP: Thanks Nicole, so to start us off, Dr. Anne Eder, who is the acting Deputy Director of OBRR, will provide us an overview of OBRR and what we'll be touching on today.

DR. EDER: Well, good morning and I add my welcome to Dr. Verdun's. We're glad to see you all here, glad you're participating. I am the acting Deputy Director in the Office of Blood Research and Review. And I'm going to give an overview of our office, OBRR, and device regulation and set the stage for today and tomorrow.

I'm going to talk, I'm going to introduce you to OBRR and talk about how we

regulate devices in OBRR, share the role of guidance, advisory committees, and standards, talk about what's new and what resources are available for developers, and provide a roadmap for today's meeting and tomorrow's meeting. Today's workshop.

So OBRR. So the organization of FDA is shown on this slide. FDA comprises centers. We're in the center of Biologics Evaluation and Research, so all biologics and related devices are regulated by CBER. In CBER we have several offices. We're in the Office of Blood Research and Review, or OBRR.

Most of our speakers today are expert reviewers and researchers in OBRR, but we also have participation from our Office of Compliance and Biologics Quality, or OCBQ, and the Office of Tissues and Advanced Therapeutics, or OTAT.

A deeper dive into OBRR, you just met Dr. Nicole Verdun who is the Director of OBRR. We have two divisions, the Division of Emerging and Transfusion Transmitted Diseases led by Dr. Hira Nakhasi and Dr. Peyton Hobson, and the Division of Blood Components and Devices led by Dr. Orieji Illoh and Wendy Paul.

And the speakers today are in the review, all our speakers today are in our two divisions, in the Review and Research branches.

This slide shows the devices related to blood and biologics that are reviewed by OBRR. In the Division of Emerging and Transfusion Transmitted Diseases, we have the blood donor screening tests and supplemental tests. Most recently the licensed *Babesia* test, but also HIV, Hepatitis B, Hepatitis C, and other usual suspects.

The source plasma donor screening tests and retroviral diagnostic tests for HIV and HTLV. We're not going to be talking about the retroviral diagnostic tests today. This workshop is focused on blood, blood transfusion and devices related to blood.

DBCD regulates blood grouping reagents. Reagent red blood cells and antihuman globulin that are used in pre-transfusion compatibility testing, as well as the automated immunohematology analyzers, the molecular erythrocyte typing tests, the human leucocyte antigen, human neutrophil antigen, and human platelet antigen, the HLA, HNA, and HPA antigen and antibody test kits, and tests used for bacterial detection of platelet components.

In addition to our office, other offices in the Center review or contribute to the OBRR submissions. And these include, just to give a shout out to the Office of Biostatistics and Epidemiology, or OBE. I've already mentioned OCBQ. And they will be addressing manufacturing CMC quality systems lot release compliance, adverse event reporting, labeling and inspections.

The Office of Tissues and Advanced Therapy, or OTAT, in this workshop to address cadaveric claims related to heart beating or non-heart beating donors. We also have participation and support from our Center for Biologics and Radiological Health, or CBRH, with respect to CLIA categorization.

Okay, so regulation of devices in OBRR. First I want to point out that in vitro diagnostics are medical devices according to the definition of devices in the Food, Drug, and Cosmetic Act, or also known as the Act.

And the IVDs, it's important to understand that these medical devices include reagents, instruments, and systems used in the diagnosis of disease or other conditions in order to cure, mitigate, treat, or prevent disease. So not only diagnostics but screening tests and monitoring tests.

They are intended for use in collection, preparation, and examination of specimens taken from the human body and the medical devices I've already said are governed by

the Food, Drug, and Cosmetic Act. And they may also be considered biological products subject to another act, the Public Health Services Act.

So the CBER devices are different in that respect from the CBRH devices in that most OBR devices are regulated under these two acts, the Public Health Service Act and the Food, Drug, and Cosmetics Act, and two related, and two sets of regulations.

For the Public Health Service Act, blood and blood products are the therapeutic, are considered therapeutic biological products and the tests used are to ensure that that blood is pure, potent, safe, and effective. And it's regulated in the CFR, the Code of Federal Regulations, 21 CFR in the 600s.

Under the Food, Drug, and Cosmetics Act, in vitro diagnostics devices for biologics are regulated under 21 CFR 800s.

Okay, device review is based on the intended use. And the intended use statement answers what indication is the device used for, what population, what samples, what mode of operation, and what other clinical information is important.

This slide shows the generic, genericized as an example of an intended use statement to demonstrate that this test, that this statement names the instrument, the analyte, and the sample. It states the indication for its use and describes any limitations for what it is not intended for use.

The basis of premarket device review is based on safety and effectiveness. That is, that there's reasonable assurance that a device is safe and effective when it can be determined based on scientific evidence that for safety in short the probable benefits to health outweigh any probable risks. And for effectiveness that the use of the device for its intended uses and conditions of use will provide clinically significant results.

When you think about risks related to a test or a device, this slide just demonstrates what it is exactly we're talking about. What do you mean by a risk when you're talking about a test or a device?

And if a test or a device doesn't function as it's intended and gives falsely negative results or falsely positive results, in the case of a false negative result for the types of devices that we regulate, a wrong device, a wrong result in compatibility testing could result in the transfusion of incompatible blood to a patient causing hemolytic transfusion reactions and worse outcomes.

And of course a falsely negative test in an infectious disease screening test could result in transfusion of blood from an infected donor causing disease in the transfusion recipient. False positives are also considered to be associated with risks, to of which are demonstrated, are illustrated on this slide.

So an Rh positive, falsely positive result, if a woman is Rh negative and pregnant could result in her missing a RhoGAM or RHC immunoglobulin shot and possibly developing hemolytic disease of the fetus during pregnancy with consequences to her infant.

For a falsely positive infectious disease result, this could result in follow-up testing, additional diagnostic studies, and unnecessary studies and psychological stress to the donor. Okay.

This slide provides a general overview of the different device classes, of the devices and their classification and the regulatory pathways used to evaluate their performance.

So this is really the overview, excuse me, the overview of the regulatory pathways for our devices, which are classified as Class I, II, III, or biologic license applications. Showing in this table, this is a good summary table because some of the nomenclature can be confusing, to

outline the decision that's made for these devices, the marketing authorization standard, how the risk-based inspections, interactions, and the timed decisions.

And I'll call out an important distinction between approved and cleared, cleared and approved. So Class I devices are neither cleared nor approved. They are marketed, they are usually exempt, but still regulated. They must be registered and listed and comply with cGMPs. Inspections are performed in a risk-based manner.

For Class II devices, 510(k) devices are cleared on the basis of a predicate, on the basis of substantial equivalence to a predicate device. So these are inherent claims of their performance. So cleared refers to a 510(k) and substantial equivalence.

Inspections are post-market. The interactions that occur during the submission are interactive review or IR, and additional information or AI requests and the time of decision is ninety days.

Cleared is not the same as approved. Class III devices are pre-market approval, so an FDA approved device implies that the submission was reviewed on the basis for safety and effectiveness.

The market authorization standard is safety and effectiveness. Risk based inspections are pre- and post-market and BIMO, and you'll hear more about those in this workshop.

Interactions during review are also interactive review and major deficiency letter, MDL. The time to decision is 180 days or 320 for panel track. And BLA, biologic license applications, these tests are licensed on the basis of safety and effectiveness.

Risk based inspections are pre- and post-market and also BIMO. Interactions are interactive review and complete response or CR. And the time to decision is ten months or six

months for a priority submission.

If changes are made to marketed devices, this slide gives you the thumbnail overview of the regulatory pathways for reporting changes to marketed devices. And they're classified based on whether the changes are major changes.

And these are changes that could possibly affect safety and effectiveness and require preapproval. Or moderate changes which are expected to have little effect on safety and effectiveness which require notification. And minor changes which are expected to have no effect on safety and effectiveness.

For a 510(k) the different submissions are shown. If it's a major change, it might be a new 510(k). If it's a moderate change it might be a special 510(k). Minor change might just require CLIA categorization.

And for PMA similarly the different types of submissions are shown whether it's a major, moderate, or minor change as for BLA.

There are, and these references are where you'll find guidances on the types of submissions that are necessary when changes are made to a marketed device. Some examples are shown on this slide just to give you an example of some representative changes to submissions that require, and their regulatory pathway.

Again, based on whether the changes are expected to have a probable major, moderate, or minor effect and the types of changes for 510(k) that might be major might be a new antibody or to remove a limitation.

As for PMA, a major change might also be a new antibody or manufacturing change, site change. And for BLA, new key reagents and also manufacturing site change. So many more examples are given in these references. These just highlight some representative

ones.

I'm going to touch briefly on guidances, advisory committees, and standards used in, that are relevant to submissions. The FDA guidance home page is found at this link and you can find the guidance documents related to biologics devices.

And I'm going to point out two that were recently finalized, that were recently finalized. One is the least burdensome guidance for your reference which was finalized in February 2019. And by least burdensome, what FDA means is that it is the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time.

The Q submission program guidance was finalized in May 2019 and it describes changes to timelines. In this workshop, there is a session in this workshop that will go into detail on the Q submission process.

These are other links to guidances applicable to devices. And I wanted to just comment that during, or in considering guidance development there are opportunities for public input and public comment either to the docket or public comment during blood products advisory committee meetings.

So BPAC is an advisory, one of FDA's advisory committees to obtain independent advice from outside experts on relevant issues. Its composition, the committee is composed of authorities knowledgeable in blood banking, medicine, and other related fields.

And it meets regularly to provide advice on issues of importance to CBER and OBRR. And so these are in a BPAC there is opportunity you can submit for to make public comment at BPAC meetings. And some examples of the types of topics that are addressed are shown on this slide.

Recognized consensus standards might be used in a device submission. This slide just emphasizes that it's important to know whether FDA recognizes the standards that you want to use in your submission. And there is a website and a database listing the standards, listing those standards. And the link is included here for your reference.

Okay, what's new and what other resources are available for developers? What's new? We expect to have product codes for BLA devices which we haven't had before. A product code is a random three-letter code, but it's important for use in adverse event reporting and searching databases. And when this happens manufacturers will receive letters with new product codes or pro codes.

Other resources for sponsors. FDA provides reagents free of charge in reference panels for development. And there is a talk in this workshop on reference panels. As well as analyte references and standards for validation and DNA referencing standards.

FDA also periodically holds workshops, also to obtain input and information about issues related to regulation of devices. And these workshops might be disease specific as was the case in the Babesia workshop, technology specific as for the next gen sequencing workshop, or education and outreach as for this workshop and the IVD round table.

Our Office of Communications, Outreach, and Development is available to answer questions. If you have questions about how to submit e-copy, about registration and listing, email user fees, other questions, OCOD is available to you to answer those questions. And I have provided their email, phone number, and contact information on this slide.

Okay. So today's meeting, I'm going to give you a brief roadmap to today's meeting. And Nicole mentioned and I just emphasized that this workshop can't be comprehensive. There just isn't enough time.

But we've selected issues that our viewers, we've selected issues that our reviewers see when they're reviewing submissions with the hope that it'll provide information that will make the submissions go more smoothly.

So for some of the elements that will be covered in the workshop, are the premarket, or, the premarket common elements. And we have speakers addressing the pre-submission INDs, IDEs, CMC, software, lot release, BIMO, and prelicensure inspection.

For premarket indication specific considerations related to infectious disease screening or donor and recipient compatibility, transfusion compatibility testing, our speakers will address from, for infectious disease screening, analytical and clinical and cadaveric claims. And for compatibility testing, immunohematology and molecular tests used for pre-transfusion testing.

In the post-market, we'll have a session on CLIA categorization, biological product deviation reporting, and medical device reporting.

So with that I thank you for your attention. And we'll turn it back over to Julia.

DR. LATHROP: Well, since we seem to be ahead, if there are any questions for Anne, feel free. Everybody understands the overview of the day. Okay. Well, we'll go ahead and move on then.

So anyone who's worked with FDA over the past several years has heard the refrain pretty constantly, submit a pre-sub for that question, come in with a pre-sub. And that's because we have the pre-sub program which is designed to help manufacturers develop their devices.

So here Iwona Fijalkowska is going to give an overview of the Q sub program of which pre-subs are a part. And hopefully you'll understand why when we say submit a pre-sub

we really mean we want you to submit a pre-sub. So, okay, Iwona.

DR. FIJALKOWSKA: Good morning. My name is Iwona Fijalkowska. I am an interdisciplinary scientist in Division of Emerging and Transfusion Transmitted Diseases in the Office of Blood Research and Review.

Today I'd like to talk about the Q submission program. Its definition, origin, and scope. About pre-submission, which is the part of the bigger Q submission program, its applicability and work flow. I'll talk about the FDA written feedback. I'll provide you with topics and examples of questions and responses.

We'll talk about meetings with FDA, what to do before the meeting, how to get prepared, and what to expect. Then I'll briefly summarize the benefits of pre-submission. Eventually I provide you with contact and references.

Q submission is a program for structured communication, for managing and tracking communication between manufacturers and FDA. It emerged from the pre-IDE investigation program. I'm sorry, I think I, yeah, this is the right slide.

This is a structured process for managing and tracking interactions between manufacturers and the FDA. It's about future applications for approval or clearance prior to their submission.

It emerged from pre-IDE program that was established in 1995. And it was instituted as a structured process in 2012 in the HHS secretary's MDUFA commitment letter. Originally the Q submission program was anchored in CDRH. Here in CBER we had our own way to early communicate with manufacturers. But over time these two programs converged and now we share this same program with CDRH.

Q submission program is broad. It contains pre-submissions, submission issue

requests, study risk determination, informational meetings, PMA day hundred, agreement and determination meetings, break through devices program, and accessory classification requests.

Now let's focus on pre-submissions. This is opportunity to obtain FDA feedback prior to an intended submission. It's totally voluntary. However, it requires formal, written application. We provide our feedback in the form of a written response. You may also request a face to face meeting or teleconference which later should be documented in meeting minutes.

Pre-submission is applicable to investigational devices or new drug applications, humanitarian device applications, master files, or special protocol assessments. It's applicable to marketing devices, to marketing applications such as premarket approval biologics license application, PMAs, 510(k)s, or de novo requests.

It also applies to accessory classification requests and CLIA laboratory improvement amendments or waiver. Later during the day we'll hear about the IDEs, about new applications as well as about CLIA requirements.

Pre-submission is not applicable to general FDA policies or procedures. It's also not applicable to review clarification questions. These questions can be readily answered by FDA staff, just call FDA and we can provide the answer without the need for a formal pre-submission process.

It's also not applicable to discuss issues that we identified while submission is under active review. For that purpose, submission issue meeting is the best way to communicate. Submission issue meeting.

It belongs to, submission issue requests belong to Q submission program, but they rule by different rules. They have different review timeframes. So please do not think that submission issue meetings belong to pre-submission. They belong to Q submission.

So the best time to come to FDA is when you consider submitting investigational or marketing application. Just to apprise us on specifics of device and to gain insight into potential hurdles for approval or clearance.

It's also good to come to us when a new device does not clearly fall within an established regulatory pathway. Be it is due to a new analyte or technology. And when you plan a study that you think might support a future application, it's good to discuss this study prior, ahead of time before you launch the study.

In the pre-submission package, the cover letter should be the main information. It should identify type of communication that you would want to have with us. It should provide the information about submitter, device name, and the contact person information.

It is specifically, it's especially important because it happens to us that when we don't have the right information about contact person, we, just the communication is kind of difficult.

It's also important that the contact person resides in the U.S. Sometimes when we need to call the contact person, different schedules for work hours or vacation schedules are not helpful.

In the pre-submission package, please also add the pre-market review submission cover letter. This is form 3514. This form, this form is entitled CDRH pre-market review submission cover sheet. However, we also share this form with CDRH and we require it to be included in the pre-submission package.

Please also specify type of requested feedback. And eventually add the specific questions. Now I'd like to tell about the pre-submission review work flow.

On day one upon package arrival and upon the receipt, FDA will assign a unique

six-digit identification number. The first two digits indicate the year and the following digits are just consecutive numbers to indicate the order of arrivals.

The assigned number is then indicated in the acknowledgement letter that FDA sends to applicants. So, for example, this year pre-submissions will be tracked as BQ19 and four digits. Q stands for pre-submission that is part of Q submission program and B stands for biologics for CBER.

The application is transferred to the right office and branch and review team is formed. It consists of regulatory project manager. This person communicates with applicant and with the document control center.

The review team also has a lead reviewer, also called committee chair, who reviews the application, performs initial RTA at least, requests consults if needed, draft responses, identifies potential issues, and so on.

When needed, we use our colleagues expertise, other reviewers or statisticians, to help formulate our feedback. By then day fifteen, acceptance review checklist is communicated to applicant.

Usually the pre-submission is accepted unless it's missing a really important part, for example, information about the device. In this case we put submission on hold and wait for submitters, for submitter to provide the missing info in the form of amendment. I'll talk about amendments a little bit later.

If a meeting was requested, we schedule it by day thirty and not later than by day forty. Eventually by day seventy our feedback is provided. We always provide you with any feedback.

If it's satisfactory and if we respond to all questions that you asked, the meeting

can be canceled. If it's not canceled, then the meeting takes place by day seventy-five. Eventually you have fifteen calendar days to formulate the meeting minutes and then we have thirty days for potential revisions.

Sometimes we introduce our revisions if we think they are needed, if some information was not conveyed in the meeting minutes as we think it should be. Other elements of a pre-submission include amendments. This could be presentation slides if you have presentation during meeting.

It could be agenda updates, meeting minutes, or meeting minutes disagreement. And this is tracked with using old pre-submission number and a, for amendments, for supplements. And here are the other elements of pre-submission supplements.

If you have new requests for feedback on the same device but on different part of the future application, be it its planned intended use or analytic plan or clinical plan.

Completely new submission numbers are assigned for subsequent requests for feedback if the device change or if the indication for use have changed.

Now let's talk briefly about our feedback, what topics can be subject to questions and examples of questions and answers. This is our advice based on the information that you provided. It includes responses to specific questions, but also we add some comments if we think that you missed something important or something needs to be extra added.

When we provide you our recommendations, these are not obligatory for you. However, for our side this advice is binding. That is so unless the circumstances change such that our advice is no longer applicable.

Pre-submission does not grant the approval, clearance, or licensure. However, it greatly facilitates the future review process.

The best topic to obtain our feedback on, regulatory pathways, device classification questions, intended use. We cannot stress it more. Intended use is very, very important because it, determines the type of study that needs to be performed in the application.

So we could comment on medical conditions that you plan to test or diagnose or screen or type of test. We do screen called diagnostic point of care. We can comment on my matrix, be it whole blood, plasma, or serum.

If you plan, and you should plan, nonclinical studies, precision reproducibility, ability cross reactivity, we can discuss this, too.

Also we can provide feedback on the clinical studies, on population inclusion/exclusion criteria, sample size, clinical size, sites, clinical reproducibility and specificity and so on.

We can comment on reference methods, on method comparison case of 510(k)s. On plans, statistical analysis. On software, cybersecurity risk management and eventually on the labeling. So anything you would want to know about the future studies to support your application just please come to us and discuss it.

Now I'd like to tell you, to show you several examples of questions that we had and how we answered them. This example is educational and information that I show here should not be extracted and applied to your device because it's out of context.

The first example, has the attached product adequately outlined a plan for addressing the recordkeeping and labeling requirements for investigational devices? Well, in the pre-submission the applicant included detailed protocols, so we went through the protocols, information about device and recordkeeping and labeling were also added. So we were able to clearly and straightforward answer, yes, the recordkeeping plan is acceptable.

In other case, the question was the following. The manufacturer of investigational device is a foreign company which requires the sponsor to import the device. In addition to FDA guidance, other specific requirements that we must align with related to this important.

Again, all necessary info was provided and we said this information was sufficient. So in this case we were able to provide the compliance program document that described in details steps need to be taken by the applicant. And we also indicated additional source of information.

Here is another example. Are the proposed internal verification studies, method of comparison, anticoagulant, interfering substances, stability, acceptable to support the proposed change.

In this case, all detailed protocols were provided. We went through them and we analyzed them. We digested this information and provided feedback. Now, the question is very broad. Due to multiple studies listed in this question, we might not have addressed specific issues the submitter was concerned about.

Really, we responded that the proposed studies are acceptable. But again, certain important information could have been missed. On the other hand, if not enough information is provided we have difficulties answering these questions, too.

For example, is the proposed stability protocol acceptable? And in this case applicant provided only the following statement. Stability testing will be performed on three conformance lots.

We assessed it as insufficient information. So the only, what we could answer was that we were unable to comment because of insufficient information. In your future submission, please provide detailed information on stability protocol and the description on

stability program.

Now I'd like to focus on the meetings, how to prepare and what to do during a meeting and after. Before the meeting, please provide several options for meeting dates. Confirm details with RPM. Set up a phone line for teleconference, confirm attendees.

If any of your attendees is a foreign citizen, we will need foreign visitor forms to be provided to us. Ideally with the pre-submission package, but not later than ten days before the meeting. This is for security and clearance. And provide the meeting agenda.

It's very useful if you prepare presentation. In this presentation, meeting topics should be indicated and questions based on our feedback. And the presentation, if you have it, should be sent to us at least three business days prior to meeting.

At the meeting, we usually limit it to one hour unless it was specifically requested in the pre-submission and justified. You should allow time for discussion and take detailed notes, which is best achieved by bringing a dedicated attendee.

Ask for clarification if needed. And at the close of the meeting, summarize action items. Please don't expect us to act as consultants. We don't discuss data in pre-submissions. Don't expect that we can clear or approve a device at the meeting.

And please don't send new questions or new discussion topics at the last minute. The way we make our decisions here is that we have entire team, we analyze carefully the information that you provide, and any decision is taken collectively and then communicated to you. So last minute questions cannot be answered.

After the meeting, it should be summarized, it should be, yeah, summarized in the meeting minutes. The entire discussion and the agreements or action items. Meeting minutes should be sent to us within fifteen calendar days and as I mentioned earlier, we have thirty more

days to introduce potential revisions.

If we do so, if we revise the meeting minutes it becomes final after fifteen days. If, however, you don't agree with our revisions, you should let us know via another amendment to the pre-submission and we'll set up a teleconference to resolve the issue. If we still remain in disagreement, then we will document it as a point of disagreement.

Now I'd like to briefly summarize the benefits of pre-submission. And they can be summarized in one slide only but the benefits are really great. And because they improve quality of subsequent application.

Early communication with us enhances transparency of the review process. It smoothens review process and potentially may lead to shorter total review times. And there is no fee associated with the pre-submission, so please come early and often as you need.

Eventually I'd like to provide the reference to the guidance document issued by FDA in 2019. All information that I conveyed here can be found in this guidance document. And if you have any question about this presentation please contact me. And here's my email address. Thank you.

DR. LATHROP: Are there any questions from the audience or from the web? No. Audience? No. Perfectly clear, thank you. Okay, so one topic that's common if you are performing investigational studies in the clinical validation of your device is the investigation of INDs and IDEs.

So Caren Chancey is going to talk about investigational applications and how they're reviewed in OBRR.

DR. CHANCEY: Thank you for the introduction. My name is Caren Chancey. I'm a scientific reviewer in the Product Review Branch of the Division of Emerging and

Transfusion Transmitted Diseases in OBRR. And today I'll be discussing investigational applications.

We're going to go through what these investigational applications are and when you need to use them for your studies. The components of the application package that you would submit to FDA. How we review these packages once we receive them. The amendments, supplements, and annual reports that you would submit to maintain your investigational applications. And finally we'll go through open protocol INDs, which are a special case that we encounter sometimes in OBRR.

So what is an IND or an IDE? These are exemptions to the regulations regarding interstate commerce which permit clinical investigations. As you can see with the highlight here, an IND is an investigational new drug application and an IDE is an investigational device exemption.

Both of these exempt from the pre-marketing approval requirements so that your product could be shipped lawfully for the purpose of conducting clinical investigations.

How are INDs and IDEs used in OBRR? So in OBRR, INDs are used for biologics and they're required for blood donor infectious disease screening devices with the exception of CMV and syphilis blood donor screening devices. These are not subject to the IND requirements.

In OBRR, IDEs are required for PMA and 510(k) significant risk studies for devices. And I'll touch on what significant risk means in just a moment. So thus in OBRR these are typically going to be HIV diagnostics, which are outside the scope of today's sessions. So I'll be focusing most of the time in this discussion on INDs.

So it's easier with these to discuss first when we don't need them. So when do

you not need an IND? You will need an IND unless your drug biologic or device investigation is exempt. The exemptions to the IND regulations are listed under 21 CFR 312.2(b). You can see the regulation for the full list.

The ones that are typically relevant to OBRR are the blood grouping reagents, reagent RBCs, and anti-human globulin are exempted. Studies with approved devices are exempted if they do not involve changes to the intended use, the labeling, the advertising, or the risks of product use.

Lastly, they're not subject to the IND regulations if the product meets the definition of a tissue. These are covered under a different set of regulations, the 21 CFR in the 1200s and they're regulated at FDA by OTAT rather than OBRR.

When do you not need an IDE? Similar to INDS, IDE exemptions are listed under 21 CFR 812.2(c). The list is fairly similar, though I advise you to check the regulations if you're not sure. The studies may be significant risk or non-significant risk.

And IDEs are required for significant risk clinical studies only. And the key element of the definition of significant risk that is applicable to OBRR devices is typically that they present a potential for serious risk to the health, safety, or welfare of a subject.

Most device studies are considered nonsignificant risk under IDE regulations and as such are subject to an abbreviated approval process. You may request study risk classification as a Q sub as you just heard in Iwona's presentation.

And when do you need your IND or IDE? You need it before you begin your clinical study. You will need it if your study involves a new device or if your study with a currently licensed or approved device involves a new patient population, increases the risks that are associated with use of your device, or is intended to support a labeling or advertising change

for the licensed or approved device.

You may request an interact meeting or pre-submission feedback depending on where you are in your application timeline as you prepare your study. And you'll hear more about Interact later, but this link here has further information on Interact meetings, which are for products that are very early in the development process.

Some additional regulations other than the IND and IDE regulations also apply in investigations. These are 21 CFR 50, which is protection for human subjects and informed consent regulations. This regulation provides requirements for informed consent for human subjects and also additional safeguards for pediatric subjects.

21 CFR 54 covers financial disclosure of investigators. This regulation requires disclosure of certain financial arrangements between sponsors and clinical investigators to minimize bias and allow FDA to assess data reliability.

Last, 21 CFR 56 covers institutional review boards. This covers standards for composition, operation, and responsibilities of IOBs that review FDA regulated clinical investigations.

So next we're going to go through components of your investigational application package. The entire list is covered under 21 CFR 312.23. I'll go through these briefly since it looks like we have time. And we'll spend more time on the items in this list that are bolded.

So your first item is your cover letter and the form FDA1571 which is formally your application. We ask that you have a table of contents and the two FDA forms described here, which are compliance with the clinicaltrials.gov databank and the financial statement.

Then we will discuss these further. We ask that you have the investigational plan, an investigator's brochure, your clinical protocol or protocols, abbreviated manufacturing

information, labeling, analytical data, information on any prior human experience, and your environmental assessment or a claim for categorical exclusion.

So for the investigational plan, this is sort of the summary of your overall application. And you'll note if you take a look at the IND regulations and the guidances available, which I hope that you do, that most of the language in there since it's an investigational new drug application, the language typically refers to terminology that's used with the drug.

So as we go through these, I'll try to highlight how those required elements from the regulations are applicable to our blood screening devices and what those terminologies mean when we're talking about these devices.

So we ask that your investigational plan include the name of your device and the manufacturer. We ask that you submit a proposed intended use with the infections and the analytes that will be detected. So the analyte, for instance, might be nucleic acid, it might be antibody or antigen, just specifically what your device would be detecting for the infection.

The population to be tested. For instance, blood donors, tissue donors, will it be living donors only or is there a geographic or a seasonal restriction on your study. It should include the matrix to be tested, whether you'll be testing serum, plasma, whole blood, for instance.

What anticoagulants would be used in samples collected for testing. The summary of prior human experience with the device if there is any. Again, if there's any withdrawals from investigations or marketing in any country for any reason related to safety and effectiveness.

And last, a brief description of the overall investigational plan for the next year.

The investigators' brochure is the information that is ultimately prepared for study participants.

So it needs a lot of the same information. It is written for a different audience. So this would need the name, again, of the device, the infections, and the analytes detected, a description of the technology that your test uses including a platform if it runs on a dedicated instrument, a bibliography of relevant publications. You don't have to actually include the publications at this point.

A summary of the study data that supports safe use in humans and a risk analysis of the risks that could be encountered by the subjects that are being tested. You'll need to include your clinical study protocols.

You need protocols for each planned study. So if your study, for instance, contains a protocol for blood testing and a protocol for testing samples from living tissue donors, we would need both of those protocols.

Your protocol should include the objectives and the purpose of your studies. You will need information on each investigator, so that includes a statement of investigator form FDA1572. This should include all of your investigators, sub-investigators, and research facilities.

You will also need to submit a statement of qualifications for each investigator and that's typically the CV. You'll need to include information for all reviewing IRBs. You'll need to include your informed consent.

I've put an asterisk here because the IND regulations don't explicitly require that the subject informed consent be submitted with the IND application package. However, since this involves blood that is donated we do ask to have the informed consent for the donors at this step.

We ask for the inclusion and exclusion criteria for your clinical studies, the size of your study or studies. And regarding study design, I'm not going to go into detail on what composes a good study design because you're going to hear more about that later today.

But the information we need on your study design at this stage is we need to know for blood donor screening devices how a true positive or a negative for the infection would be determined. And this may be by an FDA-approved comparator assay or in the case that this is a first of its kind assay and there's no comparator available, this could include your algorithm for laboratory diagnostic testing.

We need to know about any follow-up study plans that are planned with these subjects. We need information on your data management and statistical analysis plans. And then also what controls are to be included in the kit and any control subjects.

For manufacturing information, at the investigational application stage, we need sufficient information on design and the biological principle of operation of your device to establish safety. We do not need the full package that is submitted with the marketing application.

And you'll note at this stage the regulations refer to the in vitro substance and the in vitro product. So the way these apply to blood donor screening devices is your in vitro substance is the active component for your detection.

For instance, for nucleic acid test, this is going to be your primers and probes. For antigen or antibody tests the component that is doing the detection, the antigens or antibodies there.

The in vitro product is all of the components that are used in manufacture, so this may include buffers, membranes, magnetic beads if those are components of your product.

Last we need limited stability information. At this stage you don't have to establish stability for the full duration that you would use for marketing. We just need to have some information to show that your device is expected to be stable for the period of your investigation.

We need information on manufacturing sites and locations. We don't need full manufacturing flow charts at this point, but we need an outline of your manufacturing procedures. Especially noting cGMP compliance.

We need information on packaging and storage for the investigational product. We don't need final packaging at this point. We need information on the platform, instrument, or hardware that would be used with the device, if any. And also on the software that's used with the device, if any.

For IND components for labeling, we ask that you submit copies of your proposed IND labeling. The IND regs are not very prescriptive when it comes to labeling, especially compared to the IDE regs. So what we expect to see in this labeling is the name of the device, the name and address of manufacturer, and a statement that the device is for investigational use only.

If there is no approved test for the infection, we may also ask for the labeling that would be used for blood units that would note the use of the investigational test.

Marketing is not permitted under INDs. You may ask for cost recovery. It must be approved by FDA. This link here at the bottom has more information on asking for cost recovery.

For the nonclinical or analytical data that you would include in your application, we ask that you include analytical information supporting the safety of the device under the IND.

So what we typically request for a blood donor screening device, we ask that this include the limit of the detection of your device, calculated in whatever units are appropriate considering your technology and analyte.

We ask for reproducibility and precision studies, cross contamination, and you're going to hear more on these types of studies later in the talks today. Cross contamination, which is the potential for contamination between samples.

Also endogenous, exogenous interferents and cross reactivity. So endogenous being substances within the blood such as bilirubin or hemoglobin. Exogenous being interferents such as drugs the participant may be taking. And cross reactivity interactions possibility with other pathogens.

We ask for matrix studies supporting the performance of your device with any matrix that you plan to use for testing. And again, as stated previously, we want to see information on stability under conditions of use. This does not have to be a full stability study covering the duration of your product that you expect in marketing.

And last the regulations ask for a statement of GLP compliance.

Regarding prior human experience with the devices, if the device has been investigated or marketed previously in the U.S., we ask that you provide detailed information from that experience that is relevant to safety and/or effectiveness.

And we also ask that you include any copies of published material that relates to safety or effectiveness, whether or not these are studies that you yourself performed.

One element we run into some with review of these applications, if there is no prior human experience with your device, which is common for blood donor screening devices, we just ask that you say so when you reach this point of the application rather than just leaving it

blank. Because that's something that we'd have to go back and ask you for and that could cause a delay in review of your application or even possibly cause you to go on hold.

So to go through the review process of these applications, our overall review process as you just heard you may request pre-submissions before you submit your INDs. And as you've heard, these are very valuable for gaining feedback from FDA as you start to design your studies.

This can also include a study risk determination for IDEs if you're unsure whether your study would be considered significant risk or nonsignificant risk. Then after your submission is received at FDA, it is assigned a number then is routed to a review committee.

The process is similar to the assignment of review committee for pre-subs in that you'd be assigned a regulatory project manager, a lead reviewer, and any experts that are needed to review the components of your application.

And here the paths for INDs and IDEs diverge a little bit. Both of them have a thirty-day review process. For INDs, your study under the regulations may begin if FDA does not place your study on hold. It is the practice of OBRR to send an approval letter, but under the regulations if we don't say hold then you may begin.

IDEs may ~~only~~ begin ~~if explicitly approved~~ [corrected post-meeting: the IDE may begin unless notified otherwise]. Therefore since INDs are not formally approved, they're just not placed on hold, any changes are submitted as supplements. Under IDEs, any changes are submitted as amendments. But the process is basically the same with a different name.

Overall, our reviews of INDs are based on safety. If during IND review it's found that human subjects would be exposed to an unreasonable and significant risk of illness or injury or if the IND does not contain sufficient information to assess the risk to human subjects or if the

clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the described investigation, if any of these elements are true, then the IND application may be placed on hold and your study may not begin until these issues are resolved.

Again, since both IND and IDE reviews are based on safety, effectiveness may also be considered for INDs only if there is data on prior human use available. Effectiveness is typically not considered for IDEs.

And in addition to the safety-based decision for your IND and IDE, FDA may also in your letter provide feedback regarding your clinical trial design or technical data and also feedback on how this proposed study would support future marketing submissions. However, this feedback that we call below the line does not actually affect your IND or IDE decision and is provided as an advisory only.

So after your investigational application is approved, any changes are submitted as amendments, supplements, and then maintained through annual reports. So changes to IND again are submitted as supplements.

The types of supplements we typically get are protocol amendments. If you're going to submit one of these, we ask that you submit both a clean version and a redlined version of your amended protocol so we can quickly and easily see where any changes are.

You may also submit informational supplements that would be an update to your clinical investigators, sub-investigators, or your clinical sites. Or any changes or new technical information that you have that you believe we need to know about.

Another type of supplement is the safety report. You are to notify FDA and all of your clinical investigators as soon as possible but no less than fifteen days after you become of any, aware, excuse me, of any potential serious risks to your participants.

You are also to notify FDA of any occurrence or increase in the rate of serious adverse events or if there are new findings from other studies or testings. And last, a supplement may be submitted to your IND if you wish to withdraw the IND and conclude studies.

IND annual reports. This link at the top contains further information about how you submit your annual report and what should be in it. We basically request individual study information for each of your studies.

So if there's only one protocol, you've got one study. But if you submitted more than one protocol we need information for each one that was completed or in progress during the previous year.

We ask for the title and protocol number, the purpose of the study, the patient population, and whether the study is completed or still ongoing, any updates to the number of subjects that you've enrolled under your study, and any results that are available at the time of preparation of the annual report.

And then we ask for an overall summary of your IND studies including all adverse events, safety reports, dropouts, if applicable deaths, preclinical studies that are completed or in progress. Often you will be continuing preclinical studies during your investigational stage.

And any minor manufacturing or facility changes may be included in the annual report. However, if the changes are substantial enough that they would affect the safety of participants or the risk of use of the product, please contact us about that. Anything that substantially changes the risk may actually require a new IND.

These should also contain an update to the general investigational plan with the plans for the upcoming year. Remember when you first submitted your investigational plan you

included plans for the first year. So each annual report should include plans for the next year.

Any revisions that you plan to make to your investigator's brochure, any protocol updates that you made over the course of the year and did not report in an amendment, any foreign marketing developments including approval or withdrawal of the same product in any other market, and lastly, you have the option to include a log of any outstanding business with the FDA. This is optional and just a way to nudge FDA if you had any open questions that don't have a scheduled meeting or feedback that you would like information on.

And last we'll discuss a special case, which is called the open protocol IND. And this is a type of IND that is run to obtain additional safety data after your controlled trial has ended. So for instance if you have your full study period but there is a need to continue testing after your locking the data for that study.

And this allows your treatment or study to continue so that your subjects and controls may receive the benefits of the investigational device until marketing approval is obtained. So it is expected that if you're going into this type of IND that you are in the preparation stages for our marketing application.

All of the requirements regarding IRB approval and informed consent still apply. However, you may end up streamlining the data collection and expanding your study population.

You've heard already some information on submitting applications to FDA. So this link here contains further information on how to submit these applications to CBER. Any paper forms go to the CBER DCC and not directly to DETTD.

That website also has any, all the current information for any emergency use IND requests if you feel you need to submit one by that route.

And a few additional considerations. You will likely hear this a lot, but secure

email is the best way to correspond with us regarding your application. And it's the easiest way for us to get to you.

We also ask that you ensure that we can reach you during the review period since it's only thirty days. If we need additional information and we can't reach you or your designated contacts, for instance, if you don't have secure email and we're having to play phone tag, then your submission may be placed on hold when the action due date is reached if we can't resolve these issues.

Okay, thank you all for your attention. If you have any questions on the content of this presentation, here's my contact information.

DR. LATHROP: Thanks, Caren. Any questions or comments from the audience on INDs or other investigational applications? No. Well, we're well within time, but for the, for people who are on the web who may be tuning in at approximately when the agendas do, why don't we reconvene at let's say 9:40. We'll take a little break and come back and reconvene at 9:40 and take it from then. Okay, thank you.

(WHEREUPON, a brief break was taken from 9:21 a.m. to 9:42 a.m.)

DR. LATHROP: Okay, let's go ahead and get started on the next part of the first session. I forgot to mention this morning and we've had several inquiries, the slides will be available on the meeting website at the end of July. The slides, the transcript, and the webcast will all be available. So you can get all this later. And now let's go on and move forward.

So the CMC section is a very critical part of these submissions and is reviewed by two separate offices for the BLAs, OCBQ and OBRR. Rana Nagarkatti is going to give an overview of OBRR's review of our responsibilities in the CMC section. That will be followed by Lori Peters who will be talking about OCBQ and the elements of the section that they review.

So, Rana.

DR. NAGARKATTI: Good morning, everybody. My name is Rana Nagarkatti. I'm a research reviewer in the Laboratory of Emerging Pathogens in the Division of Emerging and Transfusion Transmitted Diseases. Today I'll be talking about chemistry, manufacturing, and controls, CMC, and I'll be sharing our perspectives on donor screening in vitro diagnostics that are regulated by OBRR.

So just to give a brief outline of my talk. I will cover briefly the applicable regulations and the CMC guidance documents. And then I'll go into the contents of the CMC. I'll cover critical areas of the CMC such as quality systems, which include design controls, process controls, and so on.

And I'll leave you with some points to consider based on examples that we have seen of frequent review issues observed in our review. And I just want to mention here that CMC is one of the largest chunks of information that we review. And it's wide and varied depending on the kind of device that we review, manual or fully automated and depending on the components that it may have.

So what is the impact of CMC across the product lifecycle? CMC is a critical component of the submission that describes the development and manufacture of an IVD in a controlled and producible manner. The keywords are controlled and reproducible.

As you have heard in the previous talk about INDs, in the INDs we require only a brief CMC section which includes materials, components, controls, and assembly. However, you should be aware that even at the IND stage, CMC is very critical.

One of the things that we want to review in our BLA is that the device has not

changed significantly from the time it was used in the clinical trials to the time that we're approving it. And these review timelines may be quite long.

So coming to the changes that are in the CMC, they needed to be reported to FDA in annual reports as mentioned by the previous speaker.

For the BLA we require a summary of contents of the CMC section in the BLA. And basically, it should read like a story. It should connect all the components of the CMC section and you should be connecting as many summary tables and summary reports that are there in the CMC. The focus of this presentation will be on serology and not assays.

I will not be covering the post-approval, post-licensure and post-marketing commitments. Suffice to say that I have referred to certain guidance documents which are at the end of my talk. And these are guidances that are for changes that need to be reported to FDA as a prior approval supplement change being effected or in an annual report.

So coming to the applicable regulations. The regulations that fall under 21 CFR 210 and 211, which are the cGMP regs, are applicable for us. As Anne mentioned we are regulated under both the FD and C Act and the PHS Act. And 21 CFR 610, regulations under those are applicable. These are specific requirements for blood donor screening devices for infectious diseases such as lot release testing. And other applicable requirements under 21 CFR 600 and 680 may also apply.

In addition, regulations under 21 CFR 820, which are the quality systems, apply. And I would like to mention that these regulations provide a framework. They are descriptive and not prescriptive.

There are two guidance documents that are relevant for us, one of which is the guidance for BLA IVDs. This was published in March 1999. And this was intended for use by

firms which manufacture any licensed in vitro diagnostic used for donor screening, blood donor screening.

Part one of this covers the CMC section for IVDs which we take primary responsibility for review. That is OBRR. And then part two is establishment description for which OCBQ and DMPQ take primary responsibility.

However, I would like to stress that this is a joint review that is conducted by both offices as Julie had mentioned in her introduction.

The next guidance that is applicable is the PMA IVDs guidance which is published in 2003. I will not cover this but I just wanted to mention that, as far as CMC goes, there is a lot of overlap between these two guidances. And there will be a talk specifically on PMAs tomorrow.

As these guidances were published in 1999 and 2003, a lot of references that are in these guidances have been updated. Parts of these updated guidances may also apply for the device CMC.

Coming to the contents of CMC. So first a few definitions. In vitro substances, these are, any and all raw materials and intermediates used in the manufacture of the final in vitro product as defined in 21 CFR 820.3(c).

And this includes information about manufacturing, testing, and validation of all intermediates. Details of manufacture and contractor. Description and characterization of the intermediates. Manufacturing processes of the intermediates. Incoming materials, specifications, and test methods. In-process testing and controls and stability.

The common issues that we see for the in vitro substances is the lack of information regarding the incoming material, specifically the inadequate documentation of, for

example, a missing certificate of analysis.

Acceptance criteria is established by the manufacturer of the component. However, because you will be the sponsor of the device and you will be manufacturing the device, you have to make sure that the acceptance criteria is appropriate according to your device needs.

These acceptance criteria have to be specific and measurable. For example, an O.D. less than .1 rather than color. Color is very subjective and it's not very helpful in terms of establishing the specifications.

Regarding in process testing, you need to demonstrate activity and potency of the intermediates. We highly recommend using orthogonal assays. What this means is that assays which are different from your device.

For example, if you are trying to show potency and activity of conjugate antibody, in that situation you would rather use a direct assay for that conjugate rather than use it in your device during qualification. And we also see issues with adherence to QC testing specifications.

Coming to in vitro products. The licensed product in its final form and all assembled supporting components. This is what constitutes the in vitro product. This includes information about manufacturing, testing, and validation of all kits and kit components and includes assay kits such as supporting buffer kits or control kits.

I will come to controls in a bit, but here I just wanted to mention kit controls positive, low positive, and negative controls, and then you have procedural step controls. These are meant for automated liquid handling systems where you want to demonstrate using a different method that the procedure has occurred and has taken place according to the intended step.

And then you have external controls. These are controls meant for demonstrating that the instrument itself is working appropriately.

Coming to manufacturing processes, you have to demonstrate process validation. This includes kit assembly and release testing, stability, et cetera. And then analytical methods and specifications.

What we commonly see is that there is a need to establish and adhere to specifications, particularly for controls. Validation data for all the processes must be included for review in the BLA. And you need to adhere to release testing protocol and specifications.

So this is a descriptive narrative of the CMC from the guidance. This is not an all-inclusive list here, please refer to the guidance for additional points to consider. And what I will do is I will cover certain areas which are critical for us; that are the design controls, process controls, and process validation, reference standards and panels. And the device master record and executed device history record.

The quality systems, facilities description, and manufacturing process, equipment labeling, and so on will be covered by my colleague, Lori Peters, after my talk.

So what are design controls? Design controls are meant to answer the following questions. Is the design of the device appropriate? Does it meet user needs, intended uses, and specified requirements? You need to establish, maintain, and document the design controls.

So what does design control cover? Design control covers design inputs. These are the physical and performance characteristics such as based on user needs, other stakeholders, and intended uses. For example, you want to see whether the sample is going to be a serum or plasma.

Design outputs, this is the result of the design effort at each stage and at the final

IVD. And design review. This is a review of adequacy and capability of the device to meet user needs.

The review process should work in such a way to identify problems. This can be clashing or mutually exclusive inputs or outputs that you observe. And this is an iterative process because during your development phase the design evolves and you have to reevaluate the design frequently. And you have to perform risk analysis.

The common issues that we see is a lack of establishment of the design controls appropriately. And these are inadequately documented. This usually happens for those sponsors who have worked in the IVD field but are now transitioning over to donor screening assays.

And then the risk analysis inadequate. For example, impact of changes to reference panels or their specifications on device quality.

So I won't go into details about design verification and design validation. Just suffice to say that all of this design verification and validation is meant to establish that the device is working as intended. And this usually happens during the early IND clinical studies.

So design controls also cover design transfer and design changes. In the design transfer, this done is to establish and maintain procedures to ensure correct design transfer into production specifications. This is a final stage of development intended to ensure that all outputs of the design review are transferred.

Design changes. This is to establish and maintain procedures for identification, documentation, validation, verification where appropriate, and review and approval of changes. The changes should be evaluated before implementation and there should be systems in place to enact future changes.

What we commonly see with design transfer is that, it's a critical step to

document the date of design transfer from R and D to manufacturing as design changes may impact clinical studies or analytical studies.

This design transfer date establishes that the design is fixed with respect to process validation. And any changes should go through the complete process of design controls, that is, input/output review verification, validation, and transfer.

So this slide summarizes what I mentioned in the previous couple of slides. And shows you the development of the IVD from concept, feasibility, research phase, development phase, and then transfer. So all of these processes are in between the research phase and the development phase.

And the transfer phase is when the design is transferred to manufacturing for process validation. All of this information is captured in the design history file, the DHF. And it is a summary of the record of all design actions from start to transfer including changes.

Usually what we see in the IND is a brief summary or in annual reports if there are changes made to the design. However, we highly recommend that we should get an update on the changes or on the design history file in the BLA also. This helps us in reviewing the BLA going forward.

An important aspect of design controls is that it is reviewed in detail during inspection. Design controls is a key component of the quality systems inspection technique.

So now that the design has been transferred to manufacturing, you have process controls and process validation that occur. So process controls, this is a description of the methods used for in process controls and this assures that the functional requirement of the final product is met. For example, testing of enzyme conjugates for purity or potency.

Process validation. This demonstrates that when a process is operated within

specified limits, it will consistently produce a product complying with predetermined design and development requirements. In this process validation, you could use statistical methods such as design of experiment to reduce variation in your process. And you need to revalidate if changes are implemented to the process.

Process verification. This is confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled.

So just to give an example to clarify these two, process verification and validation. Suppose you're manufacturing an antigen coated ELISA plate. There are a couple of options.

Option one is to measure the volume of the antigen that is dispensed. You could do this using an ultrasonic reader, which is nondestructive, easy, but time consuming and needs a hundred percent of the plates to be read using this method.

Option two is to perform ELISA and show that the results match control and panel member specifications. So this is obviously a destructive method. It's easy, less time consuming, but needs statistically valid sampling procedure. For example, the number of plates that need to be tested at the beginning, middle, and the end of the process.

And finally a different example with an automated liquid handling system. You could have a dye based volume estimation, which is easy, accurate, and fast. However, this needs to be built in to your design inputs.

Again, option one is a measure of volume which could be a process verification. However, you have issues with scale up of lot size. So if you scale up the lot size you may take up substantially more time and that might impact the subsequent steps of your process. So you need to be careful about that.

And if you use option two, which is perform ELISA, that's process validation. And again in this case if you scale up you need to revalidate for the actual scaled up lot size.

And as I mentioned, if you are going to use a dye based method that should be include in the design inputs and it's a process verification.

So coming to the reference standards and panels that are used for process validation and for final release. And you can have primary reference standard and a working reference standard.

The working reference standard is qualified against the primary reference standard, not against the previous working reference standards. And this enables primary reference standard to last through the product life cycle.

You could purchase these standards or obtain these from international organizations such as WHO. We supply some of these standards and panels through CBER and CDRH. And then you could use compendial U.S.P. standards.

However, you need to show that assay validation data using standards and this should be provided in the BLA. Another thing to remember is that the standard may be made in a different matrix than the test sample and, for example, for donor screening BLAs you have HIV, Zika, West Nile standards and you could use these under rare circumstances if the standard is in a different matrix than the test sample.

If no reference standards or panels are available, this usually happens for our immunoassay donor screening BLAs, which are for emerging infectious diseases. You need to establish in-house panel, which is usually more than three panel members. You'll hear more about this later in the second session.

And the values should bracket expected results in preliminary donor screening

clinical trials that you have. And it should cover a range of high positive, low positive, and negative samples.

You must establish specifications for these in-house panels. You must provide repeatability and reproducibility data, and SOPs to qualify new reference panel members should be included. This is for regeneration or reconstitution of the panel. Stability data for the reference standards should also be provided.

Key issues. It's critical if you're using this panel for in process testing of a final release of the kit, you should have SOPs for regeneration and reconstitution. You should procure enough to last through the product review cycle and beyond. Because these are the same panels that you would need for any CMC changes that you would come up with after approval.

Kit controls. So kit controls are tested along with samples to verify system suitability or validity of test performance. This include positive, low positive, if used, and negative controls.

You need to define the criteria for the assay run validity and this should be included in the instructions for use in the package insert. The kit control should be qualified against reference panels or standards. Again, as I mentioned in the list you should have SOPs to regenerate and reconstitute these and you should have specifications listed.

So usually what happens is that due to the overlap in qualification or specifications of some of the reference panels, some of them are repurposed as kit controls. And this is acceptable.

It is critical to ensure that the specifications in the IFU are identical across the device history file, the device master record. This is the record of all the SOPs that you're using for your processes. This includes the specifications for release of each component.

And then you have the device history record. This is the executed DMRs which are there and they are for the product that is being made. And specification in the IFU should also be identical across clinical testing facilities.

So other issues that we observe is that specifications should use raw data such as O.D. for immunoassays as a change of assay cutoff can impact interpretation of kit controls. So for example, for a low positive, if the assay cutoff increases, a low positive can become a negative.

Finally, the batch records. The device history record. So this is a compilation of records contained in the production history of a finished device. And usually three conformance lots are required, that is three consecutive lots. And thus you have three device history records.

It would help us if you include a summary table of lot numbers for each component such as for the three conformance lots that use three different lots of critical assay components. Include the expiry date of the components. Include document change history and date executed for each of the SOPs.

And this goes back to our need to ensure that whatever changes were made for the process validation, they are fixed and as per the specific design of the IVD. And, as I mentioned earlier, all of our lots, all of the lots that are manufactures must pass CBER lot release testing.

Deviations, CAPA, and so on are evaluated at inspection or as part of the DHR when we review the DHR.

So common issues, executed batch records as I mentioned must be submitted in the BLA. Again, conformance lots or the process validation lots may not necessarily be launch lots. At least one lot must be at the full scale or maximum batch size.

The use of three different lots of critical assays is key to assuring process

validation. And then as I mentioned, all marketed lots for donor screening IVDs need to receive lot release testing approval.

So to give you an overall take home message, regulations under 21 CFR 610 apply in addition to IVD cGMPs and quality system regulations. Design controls are critical and I've given you the reasons why.

And then CMC is critical during the life cycle of the product from IND studies to approval to post-marketing changes. And CMC changes need to be assessed for effect on product quality.

These are the references that I've used for preparing this presentation. And these include all the guidances for CMC. If there are any questions you can contact me at my email. . Thank you.

DR. LATHROP: Thanks, Rana. As has been mentioned more than once already, the CMC section is reviewed separately by two different offices. So Lori Peters is going to now review how OCBQ reviews their section, their responsibilities for the CMC section.

MS. PETERS: Good morning, my name is Lori Peters. I am a team lead in the Division of Manufacturing and Product Quality, also known as DMPQ for the alphabet soup of government agencies. And like I said, I'm going to give you our perspective on the CMC section that we cover for devices.

Just to orient you with my presentation, I'll give you an overview of my division, who we are, our review scope, because it is different than what the respective product offices do cover. And also I'll be giving you some tips as to the common deficiencies that we find in the IVD applications and other submissions. And these are typical things that we find that do lead to deficiency letter items.

So just a quick overview as was already discussed in Dr. Eder's presentation this morning. DMPQ is located within the Office of Compliance and Biologics Quality. And because of that, we do perform reviews of license applications and other submissions in concert with all product offices within CBER.

And our submission review includes INDs, the marketing applications, BLAs, PMAs, new drug applications, and also your post-approval supplements.

So what exactly do we cover when we look at a device application or submission? We are responsible to cover the quality systems. The design control is part of that as was already discussed. The facility, contamination, cross-contamination controls, equipment, microbial process controls, manufacturing process, and a limited aspect of it, sterilization, container closure system, labeling, package and kitting, shipping, categorical exclusion from an environmental assessment, and also the use of standards.

This list is just the high level list. It's not all inclusive. And I will have a slide dedicated to each topic as we go through the presentation.

The quality systems is a major aspect of our review and it covers the 820s minus the design control aspect. One slide typically cannot do the justice of what the aspect the quality systems covers. But this list is just the major topics that we will look at either during the review or during an inspection if one will occur for your product, your facility.

We'll look at the management responsibility, which is 820.20, in order to get a pulse of the quality management that is ongoing at your facility. We'll be delving into the equipment of how equipment is calibrated, inspected routinely, maintained, qualified, and that covers 820.72.

Purchasing controls, which covers your incoming testing for your raw materials,

components, also vendor qualification as part of your purchasing controls which is wrapped into 820.50.

Also for your product itself, the receiving, the testing, the end process testing that the device will happen occur and also final acceptance activities. How you manage a nonconforming product at your facility, how it's segregated, controlled, or release if testing is, shows it is adequate.

CAPA system, how CAPAs are investigated, if they're investigated in a timely manner. And your implementations to prevent future instances occurring. And also the labeling and packaging control which is covered under 820.120 and .130, especially the final kitting of all the components and the controls that go into those associated activities.

And I just wanted to note that BLA submissions, PMA submissions, any time the quality systems is impacted, the information provided should have a summary related to each of the quality systems and also provided the related procedure to cover that as well for review.

Regarding the facility, we are responsible to perform either complete an inspection or perform a compliance review. And the first bullet point, while it's seemingly basic in nature, it is one of the areas that causes our division to have a lot of back and forth with sponsors sometimes.

So we are asking that you provide an overview of the facilities that are used for production for, this should be your component manufacturers, where your final kit packaging is occurring, who the holder is of the device, device controls.

And provide the physical address, the FEI number, registration number as applicable. And also all the facilities should be then listed on the 356H form. We should be able to mirror up the information provided on the 356 to the information provided later in the facility

manufacturing section.

If there is an instance where we do not find a manufacture, it's not clear to us that there is another manufacturer, it could lead to a potential deficiency item. Especially if an inspection would need to occur.

So also in summary items that we typically expect is a general room area classification, where operations are being performed, floor diagrams of the facility along with the flow patterns, product, personnel, equipment, and waste.

And also a general description of the utilities that are in use for production of the device such as your water system or HVAC system. And a little more detail under that is a water system, are you, for instance, you can provide description. Are you using purified water, are you purchasing the water, and just some, how are you testing it as far as daily or weekly and also are you meeting U.S.P. limits.

So that's what we mean by a general description of your utilities. And also the facility design that you have regarding the controls should reflect the risk assessment regarding the environmental controls that you have. Is there a risk of a false positive or a false negative due to environmental conditions?

Is it acceptable for you to manufacture your product in, say, an ISO 8 area versus needing to be in an ISO 5. And that's something that should be identified in your risk assessment.

Regarding contamination, cross contamination controls, the information should include a description of the segregation, the contamination, and the controls. Facility controls, you know, are there air locks that need to be used, are there pressure differentials? And if so, provide the information associated with why necessary a pressure differential is needed or why

an air lock is needed.

Procedural controls such as line clearance, especially if there are multiple products being manufactured in the same area or in the same room. How is contamination or cross contamination prevented from the use of dual areas?

What are your sanitary controls? Gowning, for instance. Is it acceptable for operators to be in street clothing or do we need, or do your operators need to have, you know, hair covers and lab jackets?

Facility and equipment, cleaning, what type of cleaning schedule are you following? Cleaning agents, is it acceptable to clean your facility daily or do you follow a weekly schedule? So these are just some of the background questions that we have as we go through your review.

And it's helpful for you to provide a list of the other products that are also manufactured at your facility, which kind of counters back to is the cleaning acceptable, the cleaning routine that you have and the agents that you're using because of the other products that are being manufactured as well.

And going back to the risk assessment, that should help you to determine what type of controls may need to be implemented and that should then reflect the outcome of your risk assessment.

Regarding the equipment, it is helpful to understand, have a general description of the equipment that is used in the manufacture of the components and in the final products as well. Usually a summary table listing the type of equipment, the serial number of the equipment, the room location, basic operation of the equipment, is very helpful.

It's also helpful to know if it's shared or dedicated and between what products. If

it's product contact, single use, multi-use. If the equipment is calibrated, what the routine schedule is. Or if it's qualified, for any equipment that is qualified we expect that the equipment performance qualification report and a summary information is provided in the BLA or the PMA as well. And also description of the equipment cleaning and the cleaning validations as well would need to be provided.

We also look at microbial process controls. We specifically look at bioburden and we specifically would like to know, have a description of the in process and the final release bioburden, where that sampling is occurring in the process. And also the limit for the bioburden that is permissible at each process locations in which you're sampling for.

And again, does the risk assessment support the bioburden limits that you have established within your device. And also the method validation should be provided if you are not following the U.S.P. method. If there is any type of deviation from the U.S.P. bioburden method that should be provided and also summarized for us.

And also we do review the preservative effectiveness studies and/or the microbial interferents characterization studies if these have been performed and are applicable for your subject device.

As far as the manufacturing process, the process is looked at in more detail by the respective chairing product office. However, we will evaluate the process to ensure that the equipment used is properly calibrated or qualified and is producing the product as intended.

So with that we focus on the flow diagrams of the manufacturing process and also look at the equipment that is used at each step to understand, like I said, more about the equipment side of it to manufacture the product.

And also we would look at any rework. If you are proposing to do rework the

procedures on applicable validations to be provided as well. There are some devices that you have sterilization or parts of the device are sterile. So we would ask that you identify the manufacturer who performs the sterilization.

Again, piggybacking to my original comment of putting it on 356H form and having a summary. Because we would need to do a compliance history and check of the sterilization manufacturer. And also to identify the type of sterilization that is occurring for your device whether it be gamma, e-beam, terminal. And then as appropriate include the method validation or if you are following a standard to reference the standard.

Another aspect of our review is the container closure system. So we would need a description of the container closure, the container that is used, the size, the closure, and also that was for the finished product and for products for further manufacturing use.

And with that we would ask that you provide the validation summary report which there's a whole range of testing that could be performed depending on the lid system, a torque test or a burst test or a peel test, and ask that you provide those for the finished products.

Regarding labeling and packaging kitting, these are of the final components going into the device for the labeling. We need the description of the labeling process, whether it's a manual process, an automatic, how labels are being controlled in your facility, who has access to them. And also relabeling procedures if this is something that you would like to pursue for your device.

And regarding the packaging and kitting, description of the final kit packaging activities should be provided including the facility location, room location, the equipment that is in use for this, segregation practices, especially if there's more than one device being stored in this location or being kit packed. Also line clearance, anything applicable to final kit packaging

activities should be summarized.

The release activities and finished product testing should be clearly identified and explained. And also if you're proposing the use of a desiccant for any type of moisture sensitive parts, we'd ask that you provide a method of validation and explain the situation surrounding the moisture sensitivity and the controls that you have to control, especially during shipping.

Shipping. Regarding shipping, we would need a description of the shipping containers and your transport conditions for the final packaging device kit configuration. Whether you're shipping on dry ice or if it can be shipped at room temperature, this would all need to be explained. And also what the transport duration would be.

We need to be provided with a summary validation report. And studies can be performed either in real conditions or simulated conditions. And if you're choosing to do simulated conditions, it should represent the worst case conditions.

Typically as we explain, you know, the coldest January day or the hottest July day, which might be today. Or later this week here in Maryland.

We recommend that you perform stability testing on your samples prior to and after shipping as part of your validation activities. That way you can identify if shipping has caused a change in the functionality of the device or in any of the components.

Regarding the categorical exclusion from an environmental assessment, we do have to go back and forth quite a bit with manufacturers in order to get this correct. So if you are seeking to have a categorical exclusion from the preparation of an environmental assessment, the CFR, specifically 25.31 is used for drugs and biologics.

And this can be used for biologic devices submitted as a BLA. And also 25.34 is the CFR for devices, and that would be devices submitted as a PMA. So these are the two CFR

regulations which cover the categorical exclusion that you can then claim under as noted in the third bullet.

So when you're submitting a CE claim you must state that the action requested qualifies for a CE. With reference to the correct CFR and then also the following statement would need to be provided as well: To the applicant's knowledge no extraordinary circumstances exist that would warrant the preparation of an environmental assessment. And that is directly from 21 CFR 25.15(d).

Standards. If you are electing to conform to one or more of the FDA recognized standards, you can submit a declaration of conformity. As I noted these can be submitted for sterilization if that is part of your device.

This slide discusses if you're using the same manufacturing process or you're manufacturing a second device in the same facility. It would be helpful to clarify if you're using the same facility or the same process or have the same control processes of the other U.S. licensed products.

And this could cover, you know, facility cleaning is the same, are line clearance process, procedures the same, there's no changes in contamination or the floor diagrams we're following are the same, we're using the same type of utilities, the water system is being used.

So it can help to streamline and narrow the review process as well. And also that goes into if there is any changes to the quality system procedures or if the quality systems are the same as what is already been approved and reviewed.

And if there's no changes, the CAPA procedure, for instance, is not changing because you're introducing a second device into your facility. The procedure, a summary would need to be provided, but the existing procedure would not necessarily need to be provided in the

new application.

And if there's any changes from the U.S. license product, you would need to list the changes and provide all supporting documents.

For supplements, oftentimes we find that the incorrect reporting category is used and oftentimes we need to bump up a supplement. So we just want to reference you to the correct supplement guidances for CMCs, for BLAs, and for PMAs. And I'd just ask to consult these guidance documents in order to help you choose the correct supplement regulatory pathway.

And this slide is a summary slide that identifies the common deficiencies that we have seen in device submissions within DMPQ and oftentimes result in comments being sent on deficiency letter. And the first and the biggest one is missing or incomplete quality systems information from either the BLA or the PMA.

Oftentimes we'll have summary information but the procedure won't be provided and it's hard to connect the dots. Or sometimes only parts of the quality systems are provided. And oftentimes this leads to numerous deficiency items.

Again, going back on incomplete list of manufacturers, of raw material suppliers, design controls holders, sterilization companies. Again, a summary of what the manufacturer, who the manufacturer is, their address, FEI number and registration again should mirror what's in your 356H form, should be provided.

Oftentimes the table of contents is a little, can be unclear and you cannot quickly reference the location of studies. Sometimes the volume numbers are incorrect. And we're looking for a study and it might be located in, let's say in the clinical section which sometimes it just happens during, as you're assembling your application. So we'd just kindly ask that you

have a clear and concise location.

Another problem we sometimes see is providing data without summary explanations of criteria and results. We call this the data dump. And if we get a large amount of data that is unexplained that has no criteria, we will ask for you to retablelize it and provide it back to us.

And that could take significant time on your part then while the clock is ticking. So we ask that you clearly provide us with summary explanation of this type of data and information.

All documents and diagrams must be in English and also legible. Sometimes when diagrams especially are coming from our European colleagues, not everything is translated and we cannot be responsible to translate and understand floor diagrams.

And also make sure they are legible. There is only so much we can do with the Adobe zoom button and also magnifying glasses to read your flow diagrams. So please do a quick check of them. If you cannot read them, we will not be able to read them, so please make sure they are legible before they are sent in.

Deviations, whether it be from process or equipment, should be thoroughly explained and how it has been resolved. Equipment qualification summary reports are sometimes not provided, and this is critical information that we will need to do our review with.

And also for device supplements we sometimes find the use of incorrect reporting category and that is usually requires, sometimes we find it requires it to be a bump up in category, which is unexpected for the manufacturer and causes sometimes, you know, you're expecting to have a thirty-day notice and it's how a hundred and eighty-day notice. So it could be a difference in timeframe from what you were anticipating.

With that I acknowledge my management and also some of the subject matter experts who helped with the talk throughout my division. And that is all. Any questions, comments?

DR. LATHROP: Thanks, Lori. Any questions or comments on CMC? Thank you. So another element with a lot of information and a lot of activity and very important to many of the devices if not most that are regulated in OBRR is software and instrumentation.

So Lisa Simone will be reviewing our approach to software and instrumentation review in OBRR.

DR. SIMONE: Thank you, Dr. Lathrop. Hi, my name is Lisa Simone. I am from the Division of Emerging and Transfusion Transmitted Diseases. I work in software review policy and program activities for software instrumentation, a variety of related activities. And today I'll talk to you about software and instrumentation review and give you a little overview of cybersecurity.

This is my presentation outline. I'll provide you a systems level approach to review. I'll give you some baseline topics for risk based software and instrumentation review. And then I'll pivot to some of the newer topics which are challenges for the current use environment. And this is interoperability and cybersecurity.

And then I'll provide some updates to the software, or the premarket cybersecurity guidance which is currently in progress.

The submissions we receive come in a variety of configurations. The systems include several parts to meet the intended use, and this is a sample diagram of a screening device that's relatively straightforward with an instrument, user interface. It may include some middleware and a pooler. And there may be interactions through a firewall to a laboratory

information system and maybe the medical device manufacturer's service link.

Relatively straightforward. These may come in different configurations and they may support different workflows. Some may interface to different networks. These are relatively straightforward and all the components may come from the same MDM.

Systems can be more complex with multiple parts and connections. And you can see here this is a more complicated example where there may be more than one instrument with a user interface. We may add a preanalytical system. There may be a database server for the information. There could be communication or notifications to a mobile. Through the firewall you may have an add, a laboratory automation system. So it becomes a little more complex. And the regulatory requirements for each of these components may be different.

Our premarket review considers how each of these components contributes to the overall risk of the system. And for the review, additional systems level information may be needed to demonstrate how all parts together are reasonably safe and effective.

Now for this diagram I haven't drawn any connections among the components because it's really your architectural decision how they're going to be connected. But you can see that interoperability among these components becomes rather important.

The next few slides will give you an overview of documentation that's necessary for a software and instrumentation review. And I'm sure most of you are probably familiar with our most common guidance document, which is the Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.

We often refer to this as the software guidance, even though the scope is really larger than just software. But on the right-hand side you can see eleven items that are described in the guidance document, and these are elements that you would provide for these instruments.

But because these devices operate in an increasingly complex environment, we reference other guidance documents. And I've listed here the cybersecurity guidance documents and also the newer interoperability guidance document. The links for these are on the bottom and I've also included a page at the end of my presentation that has a list of even more guidance documents that might be appropriate for your device.

Throughout this presentation I've got a number of slides that list issues that we've observed with past submissions, so we're hoping that giving you information on these issues will help you provide more complete submissions going forward.

This slide references issues with the documentation package itself. Sometimes the cover letter doesn't describe the true reason for the submission. And in this case, it may be difficult to identify the specific changes that are the focus of the review.

Sometimes documentation is difficult to search. Hyperlinks may be missing or they might be incorrect. So we request that you check the links in your .pdf creation to allow a least burdensome review. And we also ask you to use helpful filenames.

This one hearkens to my colleague who just spoke, Lori. Complex tables are sometimes rendered into microscopic .pdf formats. And we understand that might be the case with your traceability documentation where you've got a number of columns or maybe your risk documentation. So we ask you to review that documentation for readability.

Now how is this documentation that's requested in the guidance document actually used? Our goal is to focus on what can go wrong in the system and identify what you've done to reduce those risks to acceptable levels. But I want to point out that this is not a checklist review.

Even though we've asked for these eleven items, we don't go through these items

one by one and just make sure that you've provided something in a document with that name. We actually focus on the risks and use those risks to help us decide where we search for information in your submission.

Our goal is to establish a reasonable assurance of safety and effectiveness, but we'd like to do it in a way that's least burdensome for both you and for us.

And in the next few slides I hope to give you information so that you can determine ahead of time whether or not the documentation you provide will support a risk-based review.

There are a few important questions that we ask. First, is the system doing the right thing? In other words, does it satisfy its medical purpose? And a significant amount of evidence you will provide comes in the form of your clinical trials and your preclinical trials which is outside the scope of software and instrumentation.

But there's a second very important question, too. And that is, does the system not do the wrong thing? In other words, does the system detect and prevent error situations that could cause incorrect operation? And this is a critical aspect of our risk-based review.

This is how your review staff approaches the documentation you provide. First we ask a basic question. We want to learn what the system does. And to do that we look at specific pieces of documentation.

We look at your intended use, we look at your software description, we look at the device description in the submission, and we might dig around in the manuals to figure out how you tell a user to actually interface with your device.

Then we ask how does the device do it? What is the technology behind the operation? And this information is generally spread throughout your submission, but many times

we'll go straight for the architecture document to look for how all of these different components are identified and how the components interface with one another to get a broad level of understanding of the system.

Then we'll look at the requirements and your specifications and we may also look at non-software sections to understand the scope of the technology and the use.

Once we've got a good handle on what the system is supposed to do, we look for how harm can occur when the system is used. We look at your device hazard analysis and your risk documentation and we identify issues that have higher estimates of risk. We want to focus on where those harms can occur.

Next we'll identify the specific risk control measures that can reduce the risk of harm. And your risk documentation often will point directly to the requirements and the specifications of these risk control measures.

Then we'll look at the testing you've provided that demonstrates that these risk control measures have been verified. Often your risk documentation will point directly to verification and validation individual test cases or it doesn't have to as long as your traceability matrix links all of the risk to the requirement specifications and V and V information.

This is why it's important that the traceability document is legible.

We also review the higher residual risks in light of the risk acceptability criteria that you define for us in your submission.

We also look for other sources of risk. These may be in your unresolved anomalies where you describe the anomaly and you describe the impact on leaving that unresolved anomaly in your marketed system.

We'll also look at your revision history information. For example, changes that

you may have made over previous versions. We'd like to see what those changes are, what the impact is on operation of the device, and look to see whether or not you've tested that appropriately.

This slide shows some changes with, or some issues with device hazard analyses that we've observed in some submissions. The first is risk management process is not provided or it's not explained.

And if this happens, then we can't evaluate your residual risks, we can't evaluate if they're acceptable. So for this and many of the other issues, we ask you to align with some industry standard process.

Sometimes estimates of risk prior to risk control or risk mitigation are not provided. If this is the case, we can't identify which risk control measures are the most important for reducing risk. And since we're trying to do a risk based review, we want to focus on where that high risk of harm occurs in the system.

Sometimes there's not a clear trace between the individual risk control measures and the verification testing. So that testing may be missing or it may be incomplete or the traceability itself may be incomplete. Then we can't link the requirements to the testing to make sure that the testing is reasonable.

Sometimes the risk analysis is only limited to some parts of the system, and then we can't draw conclusions about the overall safety and effectiveness of the entire system. So we ask you to provide a systems level analysis.

Sometimes the impact of hardware changes from previous submissions or hardware changes during a trial are not discussed. So we ask you to remember that the device hazard analysis is a larger scope than just the software hazards.

This slide shows some issues with the assay hazard analysis. Sometimes the specific assay hazards and harms are not included and then we can't tell whether or not you've included the assay specific hazards or those hazardous situations in your analysis.

And it may be that the same instrument can be used for different intended uses or different populations or different assays and we'd like to know your analysis. For example, typical situations or worst case situations.

Sometimes MAUDE adverse event data is used as an estimate of probability. Now use of the MAUDE adverse event data is great for identifying hazard causes, what could go wrong in the instrument, or for contributing factors. But it shouldn't be used for estimates of probability.

There are two issues. Primarily data quality issues, FDA doesn't go through the MAUDE database and make sure that everything in the database is actually correct. And we also recognize that there are issues with underreporting. So if you use this as a numerator, for example, to create a probability estimate, then you run the risk that your probabilities will be underestimated and your risk might not be controlled.

Sometimes risk acceptability criteria is not provided or benefit risk justifications are missing if those benefit risk justifications are needed. If this occurs then we can't evaluate whether or not your residual risks are acceptable. So benefit risk determinations for individual risks may be necessary. And if they are, just provide that assessment.

Sometimes factors that are outside the manufacturer's control are used to reduce estimates of risk in the device hazard analysis. So we'd ask you to remember that there are some factors such as viral inactivation or the presence of disease treating drugs that inform benefit risk discussions. But that happens after your device hazard analysis and these shouldn't be used to

actually reduce the risk estimates during your device hazard analysis.

And finally software may be upgraded during preclinical or clinical trials. And this is okay, this is appropriate to do if necessary as long as the changes, the risk assessment changes show that there's no impact on the data previously collected.

And if you do have an issue where you need to change something about the instrument during a trial, then just use the pre-submission process pathway and then we can answer that question for you.

These are some issues with testing. And the first is test plans or test protocols are missing. And we may need to look at actual test plans or test protocols to look at the type of testing that was performed especially for higher risks.

So it's not good to give us a test results document that's just full of a lot of test case I.D.s and then another column that says pass, pass, pass, pass, pass. For the higher risks we want to understand exactly what passed and how you tested it.

Sometimes there's an issue with missing verification of your information for safety. Now information for safety you remember is one of the three risk control measures that can be used. So remember that any type of risk reduction needs to be verified.

So if you're using labeling as a risk mitigation measure, you need to verify the labeling works. And that could call for usability testing.

Sometimes failed tests are not explained or they're not justified and then we can't determine the impact of these failed tests on the safety and effectiveness. So please provide that assessment.

And this is a collection of other issues we see. Sometimes unresolved anomalies don't include the impact on safety and effectiveness or on operator usage or on human factors.

And if this is the case, then we can't determine the impact of leaving those defects unresolved in a marketed system. So we ask you to provide a justification for each unresolved anomaly.

Sometimes it's unclear how the end user is notified of anomaly-related workarounds, and then we can't assess whether or not these have been disclosed to the end user. So include traces in your labeling to show where that information has been disclosed.

Sometimes full documentation is not provided for standalone software or SaMD, software as a medical device. And remember that the review must consider risks that are related to all uses of software in the system.

Now I'm going to pivot a little bit and talk about some changes in the use environment and challenges operating in the use environment, and this is interoperability and cybersecurity.

Interoperability is when two or more products, technologies, or systems exchange or use information. So what type of information can be exchanged? Patient data, assay data, instrument data, command and control over different parts of the system, mobile notifications, for example. And these are not comprehensive lists.

And for what purpose is this data exchanged? It might be to support the actual intended use of the device. It could be to receive software updates, to perform backup and restore, to do service and maintenance. So a number of things can happen. But an important takeaway message is that all of this kind of activity leads to increased risks.

I'm sure that you've seen in the news lately a number of different cybersecurity-related issues in different sectors, so it's no surprise when I say that software in connected medical device is vulnerable to threats.

Cybersecurity incidents can directly impact medical devices and network

operations. When vulnerabilities are not addressed, malware can enter and spread through a lab, a user, healthcare facility networks, and it can lead to the compromise of data integrity, confidentiality, and availability with the following effects.

There could be the compromise of critical device functionality and a delay in diagnosis or treatment and intervention.

This slide gives you a quick overview of the two guidance documents that are associated with these two subject areas. And it just gives you a bullet list of the type of information that the guidance documents recommend be provided. But, again, go take a look at the full guidance document.

For the interoperability guidance document, it recommends that you consider every electronic interface, specifically any externally facing electronic interface, like USB ports or network ports. And for each one of these you consider a number of different items.

The purpose of that interface, the role and anticipated users of that interface. Basically, what are you plugging into that thing? What's the impact on device performance? How is the interface used? And what are the limitations of that interface?

The guidance document also recommends you provide a risk analysis that includes the security-related issues. Now this doesn't have to be a separate risk analysis, it can be included in your existing risk analysis. But it's a topic area that should be included.

Include verification and validation under normal and abnormal conditions that are reasonably likely to occur. So think about connecting in a cable and bad data comes in. Can your instrument handle bad data? Or what happens if your instrument is actually sending bad data? What are you doing to maintain that interface?

And also include information on the labeling that will go to the end user so they

know what they're supposed to do with these interfaces.

This is a bullet list of information in our existing premarket cybersecurity guidance document and it's going to be updated. But this is what is in effect now. We ask manufacturers to provide a hazard analysis that's related to intentional and unintentional cybersecurity risk.

Provide a traceability matrix that links the cybersecurity risks to the controls. Provide a summary plan for your plan to provide validated software updates and patches. And then recommended security controls, like your antivirus or your firewall. I believe I skipped one there. A summary of the controls that your medical device will maintain its integrity throughout the design and release.

And these are some issues that we observe with interoperability. And the guidance document has only been out for a few years, so we recognize it takes a little time to get started. But a primary issue is some manufacturers believe that the interoperability guidance doesn't apply to your device or your system.

But take a look at the guidance document. It drives the risk identification of all functionality that are part, that's part of your system. All of the different components in your system. And the analysis should include unintentional misuse and malicious use.

So even if you have a system that has components that may not individually be subject to premarket review, if it's part of your system you still need to consider how that component affects the intended use of your system and the safety profile of your system.

Sometimes the list of externally facing electronic interfaces is not provided even though you do give a list of all of your hardware and all of your interfaces and all of your USBs. Well, we want to know if you've got five USBs on the device. What are those USBs used for

and what's the risk profile associated with each one? What have you done to make sure that nothing's going to go wrong if someone sticks an infected thumb drive in your USB?

And finally, connected functionality is mentioned without reference to your electronic interfaces, their protocols, or their protections. So this hinders our review of the risk and cybersecurity condition considerations. So we ask you provide that information.

And this slide gives an overview of some cybersecurity issues. Sometimes we don't get the diagrams that have identification of all your system components, and these might be network diagrams or data flow diagrams.

And we recognize some of these diagrams are similar to what you already provide in your architecture. Or you may have architecture diagrams that you enhance with additional cybersecurity information, and that's fine to provide the same thing in both parts of the submission.

Sometimes the cybersecurity controls are not linked to the actual risks. You might give us a list that says we're using a firewall, we're using this, we've hardened the system, we've got a white list. Well, that list of controls is great and we need it, but we also need to know what are the risks that these controls are supposed to control.

Sometimes cybersecurity is treated like a silo. We might get a risk analysis that has one line item that says cybersecurity. Well, that's not really helpful because we're looking at all the other line items that might also be compromised because of a security issue. So we want you to include that information throughout your risk assessment.

You can have a separate risk assessment document and a separate cybersecurity risk assessment document as long as there's some sort of cross reference or description of how they relate to one another.

Sometimes the worst case scenario is not assumed for a security risk. And what I mean by this is if you tell us that data could be compromised, then you should assume that the data can be changed to the worst possible value. For example, a negative result is changed to a positive result or vice versa.

And finally, low hanging fruit. Sometimes we see that there's not hardening in the system to prevent access to unused ports.

Some other issues include not disclosing the residual risks to users to inform their own risk management decisions. And remember FDA recommends that cybersecurity is a shared responsibility among all stakeholders.

Sometimes we don't see consideration of end of support dates for operating systems. Or not considering security risks associated with the use of off the shelf software, and therefore not validating that off the shelf software for security in addition to safety and effectiveness.

This is a snapshot of FDA's involvement with cybersecurity since 2013, and I'm not going to review the entire slide but you can take any of these items and plug them into a search engine and you'll find more information on our website.

But we've been involved in development of guidance documents related to cybersecurity, some safety communications. We've hosted four public workshops in this number of years. So cybersecurity is really a big issue in FDA in the last few years.

And we continue to be concerned about vulnerabilities that are identified in medical devices. Our thinking has changed in the last several years based on some of these external events and based on the review of documentation that's been provided.

So some recent issues that have driven our thinking include a hackable infusion

pump that could over- or under-infuse drugs or an implantable cardiac device that might stop working or might work incorrectly.

But we also recognize that these exploits don't necessarily target your device. There may not be somebody saying I want to target this manufacturer's blood screening device. It can be very indiscriminate.

And WannaCry is a perfect example where anybody who hadn't installed a particular security update for Windows XP could be affected. So that's a legacy software issue that we need to be concerned with.

We're also concerned about issues on the horizon. For example, ransomware in the short term is still a concern. We're concerned about attacks that influence the physics of sensors to actually change their inputs or outputs values. And this might not be through an Internet connection, but directly interfacing to the sensor through radio waves or acoustics.

And finally we're also always concerned about the tampering of medical records and trustworthiness of chart data that's used to treat and diagnose patients.

This is an example of a recall situation that did not result in patient harm, but it's a good example of the issues with cybersecurity interoperability and also with the use of off the shelf software.

In this particular example, there is an analyzer. Whoa. There's an analyzer that flew right off my screen. And you got to see the red. Oh, bummer. Okay, anyway. So we have an analyzer here.

And there is a legitimate database server and this analyzer wants to store and retrieve data from a server. And it's using an off the shelf piece of software called a TNS listener. And the TNS listener routes the connections between the client and the database.

And under normal operations, this server would register with the TNS listener to allow this communication to happen. But there is a vulnerability that was identified in the TNS listener which would allow anybody who could access the network to register their own database.

So potentially a hacker could register a database. And the very obvious thing that they could do is once they've got access they could exfiltrate, or pull out all of the data that was in that database. Or they could take it one step further and they could act as a man in the middle and then modify all that data.

So what are the possible harms? The harms are associated with incorrect patient results. So we ask manufacturers to take a look at our post-market cybersecurity guidance and recommendations on information sharing and to make sure that if a vulnerability is identified in a piece of software in your device that you're aware of it as quickly as possible.

So here are some updates on the cybersecurity guidance and I see that I'm flashing there. But everybody else went so quickly so I'm going to take a couple of extra minutes. So you know that we're doing an update to our premarket cybersecurity guidance and here's a little sneak preview.

We normally don't talk about updates and draft guidances, but CDRH has already revealed enough of this information that I can give it to you as well.

So first, or second on the list, we're asking manufacturers to design trustworthy devices to add that security that it spans the entire product lifecycle. We ask you to integrate threat modeling. We ask you to use a secure development lifecycle in addition to a regular product development lifecycle. And to consider exploitability of a vulnerability rather than estimating probabilities.

In a traditional risk management sense, probabilities could be estimated statistically based on failure of components. But that doesn't really work when you're talking about vulnerabilities that could be exploited. So it's a little different way of thinking.

Finally, we're asking manufacturers to develop a software bill of materials that they would provide to FDA and provide to your end users. Because once you've got that bill of materials with the software and the version number, if a vulnerability is identified in the wild then both you and your clients and your users will know right away whether or not your device is affected.

So we're asking manufacturers to shift their mindset to scenarios beyond that traditional use environment, the traditional intended use. We ask manufacturers to engage in proactive behavior and information sharing. And FDA continues to be worried about patient harm, but especially in preventing multi-patient or scaled attacks.

Okay, this is my last slide. These are some parting thoughts for software and instrumentation review. With respect to your documentation needs, remember that the documentation must support review of the entire system for safety and effectiveness, but also for security. Because if you've got a security issue, it will affect your safety and effectiveness.

If the system contains elements from more than one manufacturer, agreements might be necessary to allow FDA to review the necessary documentation. And when in doubt, again, use our pre-submission pathway.

So this is our final ask for you. Please play your part in a least burdensome review. Review the applicable guidance documents to make sure that you're providing the right information for us. Give us a great risk analysis to drive our risk-based review.

Ensure that your verification and validation covers the highest risks at a

minimum. And anticipate what those reviewers are going to be asking you. Proactively explain any discrepancies, any failed tests, anomalies, use of multiple software versions, et cetera. And then we can reduce the number of interactions and get the submissions through quickly.

Thank you. I'll turn it back over to Dr. Lathrop because we have no time for questions.

DR. LATHROP: Thanks, Lisa. So now for something completely different, the exciting world of CLIA categorization. All medical devices are subject to CLIA categorization, even ones that are used for donor screening. But CBER doesn't do categorization of its own devices.

Instead, it's all done in CDRH and Peter Tobin, who runs the program at CDRH, is here to talk to us about CLIA categorization, what it is, what it does, and what it's used for. Peter.

DR. TOBIN: Thanks very much. So good morning, everyone. My name is Peter Tobin and I work on CLIA policy and operations in CDRH. Within CDRH in vitro diagnostics are reviewed within the Office of In Vitro Diagnostics and Radiological Health.

We're now also called OHT7, or Office of Health Technology 7. CDRH recently went through a reorganization designed to support total product lifecycle. So OHT7 or OIR is now within the Office of Product Evaluation and Quality along with a number of other device specific offices.

So CLIA or CLIA 88 as it's called, is the Clinical Laboratory Improvement Amendments and they established quality standards for laboratory testing. And one of the main elements is that tests are categorized into three complexity levels, waived, moderate, or high, depending on how difficult it is to perform the test.

And the more complex the testing, the more stringent the requirements the laboratory that chooses to perform those tests is subject to.

So there's three agencies that work together to administer CLIA. CMS is the lead agency. They administer everything basically related to the particular laboratories. They issue laboratory certificates, they collect user fees from the laboratories, they oversee inspections, accreditation agencies and proficiency testing, and they also publish CLIA rules and regulations.

CDC is involved in developing technical standards and laboratory practice guidelines. They conduct some laboratory quality improvement studies. They develop and distribute educational resources. And they manage the Clinical Laboratory Improvement Advisory Committee, which is an advisory committee that advises all three agencies related to CLIA. And meets about twice a year.

So FDA's role in particular CDRH for historical reasons is involved in categorizing tests based on complexity, so each of those three levels, waived, moderate, or high. And we review requests for waiver by application, which is one of the pathways to get a waived categorization. And we also develop rules and guidance for those two bullets above.

So if you're new to CLIA categorizations, I recommend starting with these two guidances. The top guidance, Administrative Procedures for CLIA Categorization is really the root guidance. It describes some background information as well as the submission process and review process for CLIA categorization requests which are tracked under CLIA record or CR files as well as CLIA waiver by application submissions which are tracked under CW numbers.

The second guidance is related to CLIA waiver by application requests and describes study design recommendations and other information to submit along with your CLIA waiver application.

So when are IVD test systems categorized by FDA? So the first time would be following a cleared or approved or licensed pre-market submission. So this includes both IVDs that are viewed by CDRH/OIR as well as IVDs that are reviewed by CBER.

So when we get a pre-market submission for an IVD that's reviewed by CDRH, at that time of receipt we'll actually create a CLIA record file or CR file. And then following the clearance or approval, we'll categorize that test system.

For IVDs that are reviewed by CBER, following clearance or approval we'll receive a request from CBER internally and then we'll create a CR file and notify the applicant of that pre-market submission. And then conduct the CLIA categorization.

Additionally, we'll also conduct CLIA categorization upon request. So these are optional, but they're needed to use a test system in a non-high complexity laboratory. So one of the most common times when it's a good idea to submit a CLIA categorization request is if you have a name change.

This could be to a trade name change, it could be a name change to the manufacturer, it could be a name change to a distributor. Perhaps you're distributing a product under a new distributor name and a new trade name. And that way we can get that new name information into the CLIA database and ensure that the test system is there and laboratories that want to use it know what the complexity is and can use it in that proper complexity.

Additionally, for IVDs that are exempt from pre-market review or for devices that are reviewed by CDRH, there's a few other circumstances where we may review categorization upon request such as there's something called the replacement reagent and instrument family policy, which is a modifications guidance related to CDRH regulated moderate and lower risk IVDs.

And then the final bullet is for IVDs that are legally marketed and for which the sponsor is seeking a waived categorization. And we track these as CLIA waiver application requests.

So what is categorized by FDA? So we categorize what's considered to be a complete CLIA test system. So right here it shows the definition for a test system under CLIA. It's in 42 CFR 493.2. And it means the instructions and all the instrumentation, equipment, reagents, and supplies needed to perform an assay or examination to generate test results.

So one of the key elements there is generating the test results. So there's different types of systems that we may categorize. We could categorize a manual assay that doesn't require an instrument. We could categorize something that's like a unitized device such as a lateral flow device.

Or probably most commonly we categorize an assay and an instrument together, so that would be a specific assay and a specific instrument. And if your assay is used on multiple instruments, each one of those combinations would be categorized separately.

Something that we wouldn't categorize on its own would be an instrument that requires some type of assay in order to generate a result. So we wouldn't categorize an instrument on its own because there's no specific result that can be generated solely with that instrument.

Similar, if you have an assay that's not able to be run manually that has to be run with some type of instrument, we wouldn't categorize the assay on its own. So in general we're going to come, most commonly we categorize each instrument and assay combination.

And we'll also categorize them by particular analytes. So you may have an assay that measures more than one analyte. In some cases they'll be listed sort of as a panel. That's

most common for sort of multiplex nucleic acid type tests. But in many cases they'll be listed separately for each analyte that's detected.

So one thing that's important to keep in mind is that uncategorized test systems as well as test systems that are used or off label automatically are considered high complexity by default. So that's really the reason why we do suggest if you have a test system that you're planning to go through a name change, even just to redistribute it or a name change to your manufacturer or trade name, please send in a categorization request so we can get that test system in the database.

This is most important for moderate and waived test systems because since the default is high, if you change the name for high test system it's going to be high anyway. There's not necessarily going to be any negative impacts to your users.

But we do see situations relatively frequently where manufacturers may not know to send in requests for categorization and then CMS or other inspectors may go into a CLIA lab. They're using a test system that's been renamed. They're not able to identify the complexity of it and so the laboratory may get into trouble with the CMS inspectors.

So CLIA does apply to most laboratory testing associated with CBER regulated IVDs. To see the full details, I recommend this particular CMS memo. I provided a link here. And that goes into more detail about exactly what types of testing related to blood, cell, tissue, and organs is considered applicable under CLIA.

Additionally, some IVD devices or components may be cleared or approved separately but are not categorized on their own. Or not subject to CLIA. So in particular, a couple of areas, not as maybe relevant for CBER, but things more related to CDRH.

Certain types of breath tests, pulse oximetry, skin reflectance testing such as

transcutaneous bilirubin, these are considered not to be substances taken from the human body under CLIA. And so they're excluded from CLIA.

Additionally there's also, you know, if something's not a complete test system under CLIA, some ways that we may see this for IVDs are calibration materials and QC materials. We're not going to categorize those separately. We'll consider them as part of your overall test system if they're mentioned in the labeling. But we're not going to categorize them on their own.

Additionally, sample collection kits are not going to be categorized on their own. They don't return a result. They have to be used with other components.

So now I'll just go through, you know, how do we get to a waived complexity and then follow that up with how do you get to a moderate or high complexity. So for CLIA waiver it starts with the CLIA statutory criteria for waiver, which is in 42 U.S.C. 263(a)(d)(3). And I've kind of bolded a couple of the most important elements here.

So one of the ways you can get to waiver is if you have a test that's approved for home use. So this includes both over the counter and prescription home use. Another way to get to waiver is if you can demonstrate that your test system employs methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible.

So this is the CLIA waiver by application pathway. And additionally there's also B here. You can have a device that's determined to pose no unreasonable risk of harm to the patient if performed incorrectly. That's more difficult to prove for clinical useful tests, so we don't see that used very often, but it is possible.

So a little bit more detail about the different pathways to a waived complexity categorization. So at the top here we talk about a few different ways that are called CLIA waiver

by regulation. So in addition to home use, it was mentioned in the statutory criteria, it was also nine other types of tests that are listed in the CLIA regulations at 42 CFR 493.15.

And any of those test systems similar to the home use tests don't require any additional review following clearance or approval as long as they fall into those categories. Then they'll be categorized as waived under a CLIA record file following clearance or approval.

If you have a test system that doesn't fall into that CLIA waiver by regulation categories, then you would be categorized as moderate or high complexity following clearance or approval.

So the traditional pathway to the CLIA waiver by application shown in the middle here, sometimes now called the stepwise CLIA waiver of application, starts with a marketing submission. It could be a PMA, 510(k), de novo. And then following that there would be a CLIA record categorization and at that time the lowest that we could go would be moderate complexity.

It might be the case that the device is simple and accurate, but at that time the lowest we can go is moderate. And then there would be a, you need to submit a CLIA waiver by application submission where we would review whether the test system meets the CLIA statutory criteria for waiver. And then we could categorize the test system as waived.

So more recently for IVDs that are reviewed by CDRH we have a relatively new pathway called the Dual 510(k) and CLIA waiver pathway, or Dual Submission. And these are designed for low and moderate risk devices that are subject to pre-market notification and where the ultimate intended use and goal to be marketing is to waived settings.

So they can go directly to a waived categorization right at the same time as their clearance for 510(k). And for these we do require a Pre-Submission first. We have a guidance

related to this pathway that's currently draft. We don't yet have a final guidance in that area.

And so now I'll just go into a little bit of high level information about sort of what we look for for a CLIA waiver application. And so this is essentially just a pretty high level summary of the information that's in the 2008 CLIA waiver guidance that I mentioned earlier. And there's a link here below.

And it really all goes back to the statutory criteria. So we look is the test system simple and does the test system have an insignificant risk of erroneous results. So there's a few different aspects to simple.

It's both the characteristics of the test itself, so this is things like, you know, you need to have only simple or no reagent manipulation. You need to provide essentially a direct readout of results. You know, an untrained operator can't be expected to interpret a graph or something like that. There's no requirements for waived settings on the training or experience of the users.

Additionally, as you saw in the definition for a CLIA test system, the labeling is an important piece of the test system. So it's important that you have labeling that's designed for untrained operators. And that's generally going to be at a seventh grade level, somewhat similar to what you see for over-the-counter labeling.

And we usually look to have a quick reference guide for those untrained operators, which may be a piece of labeling that may not be present for the clearance or approval.

And additionally, you need to demonstrate that the test system has an insignificant risk of erroneous results. So usually we start out there with recommending you start with a risk analysis. And that's really looking at the types of risks that are present in those CLIA waived

settings with untrained operators.

There are no quality systems for CLIA waived settings. It's waived essentially means that it's pretty much waived of almost all CLIA requirements. So unlike non-waived settings that have quality systems, in waived settings they may not have proper temperature control. They may not have proper lighting if you have a visually read test.

So there's a lot of different environmental factors as well as sort of human factors or operational issues, especially with sort of pre-analytical steps that could go wrong. So we really want you to look through all the different steps that happen in your test procedure from the beginning to when you get the result and identify what are the risks, what are the things that could go wrong.

Either because the environment's not controlled or because the operator doesn't know how to perform the test because they haven't had any type of specialized training.

And then following up with that, we ask that you conduct flex studies to demonstrate that either your test is sufficiently robust, such as it could be used over a broad range of temperatures, or it has built in fail-safe or failure mechanisms that enable the test to catch potential errors and not report incorrect results.

And then from there we also ask you to do accuracy studies within the CLIA waived settings with intended operators to fully demonstrate that your test is accurate in the hands of intended users and intended settings.

So if you choose not to do a CLIA waiver by application or if you just go through the normal process of categorization request following clearance or approval, then your test system is going to be categorized as moderate or high complexity according to the CLIA regulations at 42 CFR 493.17.

So they describe seven different criteria that you can see here and there's basically a three-point scoring for each of those criteria. So you can have a maximum possible twenty-one points.

And if you have a total score that is twelve or lower, it's moderate. So I usually say for people to remember this it's sometimes thirteen people consider to be an unlucky number. So if you get thirteen or higher it's going to be high.

And then just a quick overview of the process. Once we receive a categorization request we'll send you an acknowledgement of receipt. This will be the case also after we get the request from CBER for a recently cleared or approved product. We'll send the acknowledgement out to the applicant or the sponsor of the pre-market submission.

We'll try to resolve any issues through interactive review because CLIA categorization requests don't go on hold. And then we'll try to provide the notification within thirty days. And it'll be followed up by posting in the CLIA database that's updated weekly.

Although the categorization is effective as to the notice of the applicant. So once you get your letter it's effectively categorized.

Really the only thing that, you know, for the sort of CBER type of products, especially if you were to send in a request on your own for a trade name change or something like that, really what we need to get is we need a cover letter that describes, you know, exactly which test systems you're requesting categorization for. What are the clearance numbers for those.

It can be helpful to send in the clearance letters, but at least if we have the numbers we can look that up. And then also we need the instructions for use labeling. So this is usually the package inserts, instrument manuals.

Sometimes we may not get both of those elements, so we may have a test system that includes one or more assays and an instrument, but we were only sent, you know, perhaps the assay package inserts and no instrument manual.

So that's something we try to reach out interactively, but if we aren't able to get that information interactively then that could result in an incomplete decision. But the majority of the time the decisions are complete and we're able to categorize those tests systems.

So that's basically what we had there. And here's a general FDA CLIA email box if you have any questions. That's the best place to send them. It's monitored by multiple people within my division. So we'll try to get back to you as soon as possible.

DR. LATHROP: Thanks, Peter. So now I'd like to ask the speakers from the first session to come up and we can have some general Q and A if you've come up with some burning issues or comments that didn't occur to you at the time. I'd like to open it up right now.

Okay, just to warm things up and get things started, I've got a couple of clarifications perhaps that people might have thought of while we're looking at the web and people are coming up to the microphone.

Peter, I wanted to ask you, so CLIA categorization the devices are categorized as high, moderate, or waived complexity. And is that associated with the risk of the device as like high, moderate, or low risk devices and device classification?

DR. TOBIN: So it's not directly connected. There is a relationship, but basically, you know, they are independent. And the complexity categorization is really based on how difficult it is to perform the test, whereas the classification is related to the overall risk of the device overall.

So you can have a test system that's very difficult to perform, just maybe is, you

know, recently come out of research stage and requires a lot of training and experience to perform but actually doesn't have a lot of risk in terms of the results of the test.

Or you could have a test system that might be a lateral flow device, you know, for HIV or something like that, that there is potential risk for the device but if it can be demonstrated that the test system is simple and accurate and meets the CLIA test criteria, it could potentially be waived for use with untrained users. As long as it can meet that criteria.

And similarly for moderate, the moderate risk is high complexity. That's really, as you saw on the slide it's really based on those seven criteria which are more on how the, you know, how difficult it is to perform the test rather than the inherent risk in the test.

DR. LAHEY: Thanks. Any questions from the web? Iwona, do we have questions from the web?

DR. SIMONE: We do have one question. It's a combination of software and pre-sub that Iwona and I were just taking a look at as well. I'll read the question. With respect to software updates during a clinical trial, if there are questions regarding changes we can approach through a Q sub. What type of Q sub, a submissions Q sub, all other types of pre-submissions have a ninety-day turnaround. Could you address the timeline associated with such a Q sub?

DR. FIJALKOWSKA: Yes. If the clinical trials is ongoing, that means that application hasn't arrived in its final form to FDA. In this case if you are thinking about introducing changes, pre-submission is the most appropriate pathway to communicate with us.

So you just describe the study, describe the issues that you have or the changes that you plan to introduce, and come so we can comment to the extent the changes are acceptable in the relation to your intended use or population.

And for that we have a seventy-day turnaround, which means that you, if you

come with pre-submission with specific questions about this clinical trial, we will provide the feedback by day seventy. Then it may be followed by a meeting within five days.

And then we just document the meeting. So total, total number of days is a hundred twenty, but that includes our potential revisions to the meeting minutes. Again, from the day we receive the pre-submission up to the, you receiving our feedback, it takes seventy days.

DR. LATHROP: Just to clarify, the seventy days and ninety days, hundred and twenty days, are the MDUFA mandated deadlines which have changed in the recent update of the guidance. But of course for particularly urgent questions, even though they may require a pre-sub, there's no requirement that we have to take seventy days.

We can certainly respond sooner than that, but we will respond in no less than, no more than seventy days. But we can certainly turn it around much faster. It's a good idea to contact us with, and let us know it's coming and what the questions are going to be.

Pre-subs let us track and document the questions and things that are coming in and also if we've agreed to a particular change or something, that then is documented as our feedback.

So it's a good idea, but again if it's a very urgent situation and you really need that feedback, but you also want to document it well, let us know and talk to us and we can certainly work with you. We're not going to make you wait on your study, you know, a hundred and twenty days just because that's the MDUFA deadline.

DR. FIJALKOWSKA: If I may add something. I also mentioned that in cases where the response might be simple, you just can call us. Well, you can call us and we provide you with a quick answer if possible only when we have any trace that you are planning, you are

performing in a study and you're planning to come with a final application.

So if you have already come with the pre-submission and then we agreed on certain study, in case of discretion this would be clinical trial, clinical study, we achieved some agreement about the study. And during the study you have some questions, then you can call us because we have enough material to look at and give you the right answer.

If you are performing clinical trials without us having knowledge about that, then the quick question by phone is not applicable.

DR. LATHROP: Any other questions? Elliott?

AUDIENCE QUESTION - ELLIOTT: First thanks to everybody for fantastic talks. Very informative but also I think you displayed an openness which people need to see so that they're comfortable approaching you. So thank you for that.

For Lori and Rana, can you speak to acceptance by FDA of ISO13485? And also acceptance perhaps of the medical device single audit program? Because I thought that I saw something about a transition to ISO13485 by the fall. The document, the rules were being written. So I just thought it would be good to hear it from you all. Thanks.

MS. PETERS: Can you just clarify the ISO?

AUDIENCE QUESTION - ELLIOTT: Sure. Well, ISO13485, laboratory quality system, is used internationally. And I thought I saw something on the web that FDA was going to be transitioning, would be willing to accept an ISO13485 certification. And that might be able to substitute perhaps for the QSR, for the QSRs.

MS. PETERS: That's something we would need to get more information on and do more research and reach out to our ISO rep for that information.

AUDIENCE QUESTION - ELLIOTT: Okay, thanks.

MS. PETERS: But that would definitely be a different paradigm moving forward, so it's something we would need to take back to our management and delve into further.

AUDIENCE QUESTION - ELLIOTT: Okay, thanks. And likewise for the medical device single audit program which I think was also kind of chaired by FDA at least at one time. If having an inspection from that group would be able to substitute for QSR. That might be something that would have to be looked into as well.

MS. PETERS: Is that a post-approval audit are you talking about or would that be the preapproval?

AUDIENCE QUESTION - ELLIOTT: Post-approval, I'm sorry.

MS. PETERS: Post-approval, okay. Yeah, we in DMPQ only do the preapproval inspections of your device manufacturers if it falls under a BLA. So for post-approval, that would be something more targeted to our compliance group, team biologics or ORA.

AUDIENCE QUESTION - ELLIOTT: Right. Okay, thanks.

DR. SIMONE: If I may add to that, with respect to ISO13485 FDA has produced, FDA has produced some information online and some of that is still in progress because you know that there are some subtle differences between the QSR and 13485. And right now we do plan to continue some of these activities, but nothing is finalized at this time. So I think the official answer is stay tuned.

AUDIENCE QUESTION - ELLIOTT: That's fine. I thought I saw, there was something on the web, there was a target date for a new rule coming out in the fall. So I was just trying to understand if, oh, yes, I know that well. Thanks.

DR. SIMONE: There is another question on the web I'll take. Oh, I'm sorry, go ahead.

AUDIENCE QUESTION - DEB HINKLEY: Hi, Deb Hinkley, Abbott Labs. I have a question. Somebody had mentioned that we'll be getting product codes for the biologic products and I was wondering if you could perhaps expand on that a little bit more. Just it was mentioned that manufacturers would get a letter, but will there be a process, will they just be assigned? If we could hear a little bit more on that.

And then also if we're going to have product codes for the blood screening IVDs, does that mean we'll also be doing medical device registration and listing or are we covered with the blood screening establishment registration and listing?

DR. LATHROP: So the product codes, yes, we're very excited. We'll have product codes for BLAs. And primarily they're used in this context for adverse event reporting because right now, IVDs are, even though they're used for donor screening and for BLAs, they're still subject to adverse event reporting, which Bima Patel will be talking about later.

But there's no mechanism to report it under the proper product code at the moment. So we're in the process of updating the database and making sure it all works. Then we'll be notifying the manufacturers. New devices that have come out after the product codes have been established, they'll get the product code when they are licensed.

Otherwise, we'll be notifying, we haven't yet worked out all the details of the process and how that will be. The other question? Oh, registration listing.

I'm still subject to the blood establishment licensure issues, not, I don't believe it's going to be the new registration listing as well. We'll double check and we'll certainly let you know if there are any changes to that part.

AUDIENCE QUESTION - DEB HINKLEY: Okay, and the product codes for registering for the adverse events, is that going to align somewhat with the BPDR codes as well

or are they going to be separate? Do we know?

DR. LATHROP: They're going to be separate. They're going to be like the normal IBD product codes, the three-letter code, and Peyton will be bringing that up in his talk. Specifically for, you know, other IBDs have product codes right now, the three-letter, random three-letter code that you plug into the various databases and for submitting things and like that.

But we will also be informing manufacturers, and the questions are good questions. So if there are other questions about how it will be, the things that it might be affecting that you want clarity on, be sure and give us an email so we can make sure that when we do notify, those questions have been covered.

AUDIENCE QUESTION - DEB HINKLEY: Okay, thank you.

DR. LATHROP: So there was a question on the web, Lisa? Okay.

AUDIENCE QUESTION - ELAINE WILLIAMSON: Hi, Elaine Williamson, American Red Cross. We have a product development team for IVD immunohematology reagents, so I have some just sort of general old school questions if you don't mind.

The first one is we are having trouble locating a CMC. It's probably a very old one for three percent reagent red blood cells. We've called, we've written, we've researched, we've looked in the archives. Can you suggest a path for us to find, get a hold of maybe guidance that's sort of outdated?

DR. LATHROP: I would recommend that you give us a call and talk just about this specific issue. We understand that there are a lot of older devices out there coming in that don't have all the documentation that now we would expect. And we certainly don't expect people to go around recreating anything. But how to manage that is something that's going to take a little bit of thought, so.

AUDIENCE QUESTION - ELAINE WILLIAMSON: Okay. And for a BLA with, we're sort of a mature manufacturer, so we have previous BGR submissions. We have 510(k) submissions. So do you accept historical validations as a rule or do you need to revalidate if you use basically the same process? Does it depend on the validation itself?

DR. LATHROP: So again, I'll just jump in here. Again, specific questions for specific issues, if it's still valid and appropriate then, you know, we're open to different pathways and we're not going to necessarily expect a whole new revalidation of something that's already validated. Depending on what the documentation is.

But it does get tricky because again you have older products and stuff. So you should come and talk to us to make sure, and again, you could submit a pre-sub. Asking that question because you want information that you can rely on. We want to be able to think through all of the issues and the details. So as much information as you can give us about the situation, the better off it is and the better the answer will be so then ...

AUDIENCE QUESTION - ELAINE WILLIAMSON: So what I'm hearing is maybe the best way for us to approach this is to have a pre-sub meeting so we can ask for specifics.

DR. LATHROP: Right, because we want to be able to actually answer that specific question, which may sound similar to a lot of others but there may be nuances that, you know, are applied to you that our more general expectations would not be reasonable.

AUDIENCE QUESTION - ELAINE WILLIAMSON: Okay, and the final one I have is now with the new, you know, we manufacture non-sterile products. So are you expecting to see new BLAs that you have final container testing from microbial contamination? Or as long as you can show control and environmental controls, are you not expecting that anymore?

Because I was a little confused from the presentation.

MS. PETERS: I'm sorry, can you expand further?

AUDIENCE QUESTION - ELAINE WILLIAMSON: So it's a non-sterile product, right.

MS. PETERS: Right, it's by word and controlled, right?

AUDIENCE QUESTION - ELAINE WILLIAMSON: Correct. So are you expecting to see final container testing on a BLA?

MS. PETERS: Yes, we would.

AUDIENCE QUESTION - ELAINE WILLIAMSON: Or and a bioburden. You still are.

MS. PETERS: Yes, we would expect to see some type of bioburden testing done at final release and throughout the process if you feel that is necessary. What the specs are and also, are you asking about container closure integrity?

AUDIENCE QUESTION - ELAINE WILLIAMSON: Mm-hmm (Indicating affirmatively).

MS. PETERS: Yes. We expect to see that your device can remain adequately closed and that the bioburden is done at the limit as you specified.

AUDIENCE QUESTION - ELAINE WILLIAMSON: Okay, thank you.

DR. SIMONE: This is a question online. Is FDA enforcing cybersecurity requirements for all medical devices? This is all the information that came in this question, so it's a little challenging because we don't have requirements for cybersecurity. There's no shall for cybersecurity.

We currently have a pre-market and a post-market cybersecurity guidance

document that's non-binding, but it does encourage you to use the process that I described before. So I'm not sure exactly what's meant by requirements.

We do ask you to include it in your risk documentation because security is a new risk that needs to be considered. So we need to see that as a part of your risk documentation. And then we would evaluate how you handle those risks according to whatever process you tell us is involved.

So I'm trying to think ahead about requirements and I'm wondering if maybe the questioner was also thinking about the current draft pre-market guidance, which has been out for comment in the spring and we're now resolving those comments.

Where there have been changes to the existing pre-market guidance, where FDA is asking for some more specific testing information, for example. Penetration testing or static analysis testing. So the questioner may be thinking along those lines.

And what I can say in terms of the seven hundred plus comments that came in for that draft guidance is we've accepted at least in principle a majority of those seven hundred comments. So what you saw in that draft is reasonably close to what's going to be in the final, the guidance. And again, that's not a requirement.

But FDA will be providing more information on the types of things that we would recommend for you to do in the design of your device to address cybersecurity. And we're also providing some specific recommendations about some testing and verification and validation for cybersecurity.

So I hope that answers the question that came online.

DR. LATHROP: Any other questions? All right, then, let's adjourn for lunch. Let's reconvene at 12:30 and thank you everybody for attendance and questions this morning.

And we'll continue this after lunch.

(WHEREUPON, a brief break was taken from 11:40 a.m. to 12:33 p.m.)

DR. LATHROP: Okay, let's go ahead and get started on this afternoon's session. Thanks everybody for coming back from lunch. I just wanted to remind people that the slides and the transcripts will be available on the conference website at the end of July, so you'll have access to all of those in perpetuity about two weeks after this meeting is over.

So after CLIA categorization, now we're going to talk about some other aspects of BLA IVDs that are very interesting. Kori Francis is going to discuss the lot release program that is used in part of the pre-market submission licensure for BLAs.

MR. FRANCIS: Hi, good afternoon, welcome back. I'm Kori Francis. I'm one of the team leaders in the Laboratory of Analytic Chemistry and Blood Related Products within the Division of Biological Standards and Quality Control, or DBSQC. We're located within the Division of Compliance and Biological Quality here at CBER.

If you'd just allow me like thirty seconds to give you a quick brief background it might help you realize how we fit into the equation of lot release. I joined FDA back in 1989 as a biologist within what is now the Division of Emerging Transfusion Transmitted Diseases.

I previously performed review activity, assisted in panel development, performed inspections, and primarily performed lot release assays for the blood donor screening assays. Around 2009 during the center's quest toward ISO accreditation, my team was reassigned to what is now called DBSQC.

While continuing to perform lot release and related activities for the in vitro diagnostic test kits used for blood donor screening assays, my team also performs review of test methods and validations of several hematology products as well as the lot release activities for

these assays for these products.

We continue to maintain our ISO 17025 accreditation of several test methods used to evaluate these products, and while adhering to our quality assurance program. I was asked today to provide a brief presentation of the lot release program as it applies to the in vitro diagnostic test kits here at CBER.

As you can see here, in 21 CFR part, subpart A, the general biological product standards, no lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such a product.

Each applicable test shall be made on each lot after completion of all processes of manufacture which may affect compliance with the standard to which the test applies. The in vitro diagnostic test kits or blood donor screening are regulated by the blood, biological license application product. So therefore they're subject to lot release.

So basically upon completion of review of any lot release submission, the manufacturer will receive what's called an official release notification letter, which is generated and signed by the delegated CBER authority. Generally the director of the Division of Manufacturing, Product Quality, or the associate director or the sample custodian.

The sample custodian is basically the head of the product release branch, which is also located in the Division of Manufacturing and Product Quality, and they're responsible for the whole process from incoming samples to release of the product.

And again, blood donor screening assays are MDUFA products, therefore they're devices.

So as a quick overview of the lot release program, the lot release program is designed to provide ongoing monitoring of licensed biological products. Prior to licensure, in-

support testing samples or conformance lots are supplied to evaluate product quality and kit performance.

Post-licensure, we usually have routine lot release which requires that the samples, and sample in this context means a representative sample of a batch of the kits that are being produced, together with the lot release protocols which are submitted for evaluation to assure continuing product quality.

Protocols, or the lot release protocols contain the information about manufacturing and specifications and QC testing data. The content of each lot release protocol is established during the BLA review process.

Samples and lot release protocols are submitted to the Product Release Branch, which is in the Division of Manufacturing and Product Quality, while OCBQ manages and OCBQ manages the lot release program.

Sometimes samples are submitted prior to the lot release protocol. This may happen when some of the product testing has already been performed. But say some of the accessory testing isn't completed such as bioburden testing that you heard about this morning.

Usually the lot release sample is submitted with the lot release protocol at the same time. So basically CBER aims to complete testing and/or lot release protocol review within thirty working days of the lot release protocol submission.

Some of the older products that we have, some of the older assays, may use some generic laboratory equipment such as plate readers, incubators, rockers, pipettes, whatever. But because we follow the guidance of our accreditation, all of the equipment that is maintained within calibration dates in a state of readiness following a recommended preventive maintenance schedules.

So I say that to say that sometimes you have some unique features of in vitro diagnostic products which can impact lot release. For example, the equipment. Some of the newer equipment now are very large pieces of equipment and they're specifically designed only for the assay that the manufacturer is producing.

The manufacturer usually provides the instrument to CBER and the firm is responsible for qualification, training, and maintenance, the major maintenance of the equipment. We perform some of the maintenance, some of the PMs that are within our purview.

Sometimes the equipment is so large that the floor space becomes a limiting factor. So therefore it's not always possible to accommodate all of the equipment that's now used for blood donor screening testing.

Sometimes we have this program called a blinded panel testing where the manufacturer is given, provided with the blinded panels. These are lot release screening panels. And they do the testing at their facility.

The blinded panels are provided to the firm and the results are submitted in that lot release protocol that I was referring to before. CBER compares the results of the blinded panels from the firm with the expected results to confirm the acceptability of kit performance.

Another thing to think about is what was talked about somewhat this morning about software. During the IND phase or even during the early BLA, the manufacturing may be using an older operating, an older system of software, but the final operating software needs to be provided to CBER.

This can delay testing if we don't, if we're not provided with the actual software that will be used in the field at the time of licensure.

Also another thing to think about is the kit design. In the old days a lot of the kits

were pretty much self-contained, where all the components that were necessary to do the testing were in one kit.

Sometimes kits consist of a primary reagent kit and maybe an accessory kit or confirmatory kits in case of HBsAG where you may have accessory kits that do, for the run controls or for the calibration or for the wash kits.

Each of the primary kits is submitted together with these accessory kits or the confirmatory kit so the testing can be performed. However, only the primary kit is released at CBER. The manufacturer is responsible for ensuring that the quality of the accessory kits and the confirmatory assay kits as well.

So I just want to give you a quick overview of the role of DBSQC and DMPQ in the lot release activities. Here at DBSQC we review the test methods and the validations and qualifications of certain products. We also review the package inserts and review the instrumentation or the platforms that these test kits go, are used on.

The lot release protocol template is submitted during the BLA, when the, submitted to the BLA as reviewed and finalized by DBSQC. Before the BLA approval, equipment to perform large, to perform lot release testing is identified and if necessary obtained from the manufacturer.

Our analysts are trained to perform these assays prior to doing any lot release testing or any in support testing. Post-licensure the lot release protocols are reviewed and the confirmatory testing is performed under an ISO 17025 environment.

The requirements of the ISO 17025 is a standard, a standard that we adhere to. If blinded panels are used, the results are reported in lot release protocol and are compared with the expected results of the lot release panel.

DBSQC reviews the lot release protocol and review and testing of documents. These are documented into LIMS, or laboratory information management system.

Now one of the roles that DMPQ does is they're the host of the product release branch and the sample custodian. So therefore the samples are stored appropriately, they're logged and tracked into lot release database system. Testing is tracked in the quality system database system, which is also within DBSQC.

Once all the testing and reviews are complete, an official release notification letter is signed and sent to the manufacturer. So now we'll talk a little bit about the in vitro diagnostic product evaluation.

Licensed test kits are evaluated by reviewing a few things. One, the data provided in the lot release protocol and the results of the tests performed in the DBSQC laboratory. Or the results of the blinded panels that I was referring to a little while ago that are tested by the manufacturer.

Now the panels in this case, we're talking about serum, these are lot release, either lot release or reference panels. And they are usually made up of reactives, non-reactives, or borderline sample sera. It depends on what you're looking for from the analyte. If it's a NAT kit you'd be looking at a RNA/DNA based serum panel. If it's an antibody test kit it may just be a positive antibodies spiked serum.

And these have been developed in DETTD and in OBRR for testing of like say HIV-1, HIV-2, HTLV-1, HTLV-2, Hepatitis B core, Hepatitis B surface antigen, Hepatitis C or Chagas (*T. cruzi*), *Babesia*, West Nile, or Zika. And so these panels are used to confirm the specificity of the test specificity and sensitivity of the test kit.

Sometimes new products come along which may require the development of new

or different panels to test the efficacy of the test kit. This was an example like for, a recent example would probably be like Babesia where we did not test Babesia in the test but they've been recently licensed so we had to come up with a new panel to, panels to evaluate those products.

So now let's talk about the lot release protocols. The lot release protocol format varies by product and manufacturer. There is no standard format for a lot release protocol because each of the products that we test are a little bit different and so you cannot like have a cut and paste of exactly the same lot release protocol.

The protocols have to contain the following information. The name of the manufacturer, product name, product trade name, the STN, the facility license number, the type of container. Basically all kits are considered final container or FC, has to be noted on the lot release protocol.

The address, the summary of all the testing results, pass or fail, the reason for the submission, for instance, lot release. A signature line for the authorized official or delegate approving the submission. Only certain people at the manufacturer are allowed to submit the lot release protocol.

We also need the lot specific product information and the results of all the release tests that are applicable. There's a process to develop and change or correct the lot release protocol. Actually, it's two different things that I'm talking about here.

The manufacturer submits the lot release template for CBER's review during the original BLA process. CBER may or will ask for changes if needed during the BLA review. When the manufacturer makes changes that impact he information provided in the lot release protocol, a revised lot release protocol is submitted for review together with a supplement.

When the lot release protocol is submitted with incorrect information, that is the actual signed off lot release protocol comes in and let's say there's a typo or the wrong information was placed on the protocol. You have to, the manufacturer is then charged to submit a corrected lot release protocol to the product release branch.

When CBER reviewers identify any errors in the lot release protocol, the product release branch is contacted, contacts the manufacturer, and asks for an explanation of the corrected protocol.

So now let's move on to another thing. There's another thing that we have that's an alternative to lot release. Basically it's called surveillance. Surveillance is an alternative to the lot release program. Surveillance is only granted to products with an acceptable lot release history and demonstrated control of the manufacturing process.

The manufacturers may submit data in a prior approval supplement to support a request for the product to be placed on surveillance. If surveillance is granted, the manufacturer distributes the product lots without prior approval from CBER. That is, they don't have to wait for that lot release letter that I was talking about earlier.

Under the surveillance status, the manufacturer is still required to continue in-house lot release testing. It's also required to provide information regarding all the lots produced, usually in an annual report. But this may be requested to submit information more frequently. It depends on the amount of products that are being made.

The manufacturer is also required to submit representative samples and/or lot release protocols. Actually, it's "and" lot release protocols. At intervals determined by CBER. The lots are subject to CBER confirmatory testing and the lot release protocol is still reviewed.

If product performance or manufacturing issues are observed, CBER may direct

the return back to the lot release program. So just to give you a quick sequence of how things operate, you heard about the IND process earlier this morning. And basically at that point you're discussing how the assay works, you identify the equipment that's probably going to be used.

During the BLA process you develop and finalize the lot release protocol template. The blood and related products team, which is my section, if there's major equipment that can be installed at CBER we'll arrange to have that installed.

Therefore, we arrange to have the installation, operational, and performance qualification of the instruments before we do any testing. We also arrange to have a qualified trainer come in to train our analysts.

After training, the blood related products section performs what's called in support testing to perform kit performance and demonstrate QC testing capability. We also perform testing and review of the lot release protocol for any large lots.

Post approval, the manufacturer submits samples of each of the lots for distribution with the completed lot release protocol to the product release branch. The manufacturer distributes lots after receipt of the, can distribute lots after receipt of the notification from CBER.

So basically in summary, just to reiterate the whole sequence, is that the blood donor screening products, the in vitro tests are devices regulated by the BLA, through the BLA process. IVDs are subject to lot release requiring submission of a lot release protocol with a product or a kit sample for each lot that's intended for distribution.

Kits may not be distributed until receipt of the official release notification letter from CBER. CBER performs testing of submitted kits and reviews the results of the blinded panel test if that's applicable in the lot release protocol.

All licensed products must demonstrate that they're capable of producing accurate results, sensitivity, and specificity. Changes to any manufacturing or testing facilities or the lot release protocol should be submitted as a prior approval supplement or change being effected, or change being effective thirty days.

Any corrections to lot release protocol should be submitted to the product release branch with the lot release protocol marked as corrected protocol. The surveillance program is an alternative to the lot release program and may be approved upon review of data demonstrating consistent manufacturer and product quality that's routinely being met.

It's not a guarantee that any manufacturer will automatically be granted the surveillance program. We have to review the data for an unspecified time period. So with that, I take, I thank you for your time and your attention. Are there any questions?

DR. LATHROP: Thanks, Kori. So a key part of determination of safety and effectiveness of a device is inspections of various components of the development of the device, one of which is clinical trial sites. So Bhanu Kannan is going to give us an overview of the BIMO program here at CBER.

MS. KANNAN: Hi, good afternoon, everyone. I'm Bhanu Kannan and I thank the organization for giving us an opportunity to come and speak to you all here. And before I start, I just want to know how many of the sponsors are here, the industry folks? Okay.

So that way it's easier for me to talk about some of the violations we have seen or maybe some of the experiences that we have come across. So that way I know I'm addressing the right audience.

So I'm Bhanu Kannan and I am in the Office of Compliance and Biologics Quality. And it's called bioresearch monitoring. We normally do inspections. I'm under the

Division of Inspections and Surveillance and we do inspections pre-marketing inspections of clinical trials, namely sponsor clinical investigators, IRBs, and other NTPs.

So just to kind of orient us to what we do in this. So today I'm going to talk about our program. So have any of you been inspected by, sorry, I'm one of those people who tend to walk normally. How many of you have been inspected by the BIMO program?

Okay, so that's good. So at least you know that what we do and when we go out and do the inspections what is expected of the FDA's BIMO program. So I'm going to talk about our BIMO program in short for the bioresearch monitoring. And the type of BIMO inspections we conduct and why we conduct them.

And also like the profile off of our CBER INDs and IDEs, because we also support other products within CBER like Office of Vaccines or cell and gene therapy, so we do inspections of sponsors, clinical investigators of some of the other investigational products.

So I'm going to kind of like briefly give an overview of our products. And since we are in compliance, obviously I will be speaking briefly about the responsibilities of the sponsors, clinical investigators, and contractor TROs and some of the common violations we have come across in our BIMO inspection program.

And some suggestions for doing some successful clinical research. And obviously some of the FDA resources. So about the program, so our branch, we are a very small branch. Totally one lead of us, eight reviewers, and one branch chief.

So we are a very small branch but we wear different hats. We do inspection assignments and we also investigate complaints. Sometimes it could be a complaint coming from somebody, FDA reviewer going to a conference and then somebody from one of the industry maybe complaining to them, oh, by the way, I heard so-and-so is doing this, can you

please check this out. So we do get complaints and we investigate those complaints. It could be coming from anyone.

And then we answer questions about GCP, like whether it can be coming to our inspection mailbox or it could be coming through our office of communications in CBER. Any time there is a question about data integrity, namely somebody is faking data or making up subjects, we have had cases wherein they will have like Britney Spears as one of the study participants.

And then we have an inspection where we have seen like Martha, you know, Washington there. And basically all those, they made up those subjects and they're ripping us just for $10, you know. I mean, so we do. We do actually evaluate any time there is data integrity we go out and we evaluate the concerns about that.

And we do, like I said, we wear a lot of hats, so we also participate in a lot of guidance and other policy development working groups. And so that we understand what's going on so that we can have a voice in there. And we do a lot of outreach activities just like the one we are doing. I mean, external as well as internal outreach activities.

And so what is the review function of our branch? Namely, I already said that this is to detect errors and misconduct, namely the Britney Spears as a subject. Or it could be somebody constantly crossing out without any rationale, crossing out the data in the source document or case report form.

So we try to evaluate like any, detect any errors and misconduct in clinical trial. And why do we do this? We do this to protect the safety, welfare, and rights of the human subjects at the end of the day.

Whether it is giving samples or participating in any clinical trial for any market to

be, any product to be marketed, we need volunteers, we need subjects. So to protect their safety, welfare, and rights. And obviously for data integrity and quality.

Then the type of inspections we do. So as I said, we inspect clinical investigators, CIs, and sponsors, monitors, and CROs, contact. I mean, if a sponsor hires a third party to do part of their obligations, because regulations do allow, sponsor can transfer some of the obligations to a CRO.

Or they could even ask them to do monitoring some of the other functions, the responsibilities that the sponsor has to do to a third party. But they may still be responsible if there is a problem. So we do inspections of sponsors, monitors, and CROs and institutional review boards and the nonclinical laboratories.

And when do we do them? Whenever a BLA is submitted prior to that BLA being approved we do inspections of the BLA and NDAs and also the PMAs. And as I said, referrals from other Center staff, this could be coming from like one of the other product office and other parts of the FDA.

It could be coming from CDER or some of the other CDR, one of the other centers also. We could do inspections based on that and complaints. Sometimes sponsors could tell us, oh, yeah, by the way this clinical investigator is not following the protocol I gave.

So we get complaints so we follow the lead. And also it could be coming from ORA. I mean, there was a case where an ORA investigator, she was just driving and then she heard this commercial for a product, an advertisement. And then she's like, mmm, how come they are doing this advertisement, I know fully well this product has not been approved.

So she came and contacted us and then we assigned an inspection and obviously this was not something they were supposed to be advertising. It's not, it's false promotion. So

anyway, so we do follow some of those leads, advertisements and news reports.

And last but not the least, this is very typical of CBER. We do a lot of surveillance of ongoing studies. These are, we have done, each year we take up some surveillance inspection. We sought to evaluate the status of ongoing.

Whenever we go do the BLA inspections, inspections for BLA, the study has already been conducted, right? The sponsor has completed the study and two, three years they, you know, turn up the data and then we go and do.

So there is no ongoing study. However, the surveillance inspections are real. We actually go evaluate the status of ongoing studies. So that's very, very typical of CBER. Only CBER does, none of the other centers do them.

And sometimes it could be pediatric vaccine studies, so we have then cell therapy, gene therapy studies, just to get the status. And we have also then a lot of those infections, emerging infectious diseases like Ebola or some of the other ones.

So we do, and then this year we did our products, so we collaborate. This is some of the collaboration with the Office of the Commissioner, our product designation. We want to see how they are. If they give branch, what is the status of those inspections. So we do other inspections, too.

So now let me just orient you to the different, like the metrics of the different INDs we get. This is kind of like a chart of close to twenty-eight hundred. But as you can see, there is a good chunk of commercial sponsors for CBER. But we also have a lot of individual.

The individual sponsors are a lot of either academic sponsors like some of them could be sponsor investigators, but these are individual academic sponsors. So we do have a good chunk of them in CBER. And then as you can see, twenty-nine percent, which is really a

higher number. And then we have like government and a lot of other entities.

And this is a breakup of the chart of twenty-eight hundred, what products, right? I mean I know here this is office of blood, but like I said, we support bioresearch monitoring program, we do inspections of various investigational products.

So cell and gene therapy, that's a big chunk of them. And a lot of the sponsor investigators and academic sponsors are from the cell and gene therapy. And then the vaccines and then as you can see a lot of them, the live biotherapeutics, those are your probiotics, the yogurt that we eat. I mean, of course, if it is investigational then they need an IND.

So briefly shifting gears, sponsor and who is the sponsor and who is the clinical investigator? Your sponsor is someone who takes responsibility for initiating a clinical investigation and the clinical investigator is someone who actually conducts. Under whose immediate supervision the supervision is critical. The drug is administered and also they follow the subjects.

And sponsor investigator as I mentioned earlier, this is CBER, so you see a lot of sponsor investigators. And they have to wear two hats, both sponsor and investigator. So this person will have like have to abide by, follow all the requirements of sponsor as well as all the investigator obligations.

The only difference is there is no need for an investigator brochure. And also a sponsor investigator, it means there is only one site, that's it.

Other responsibilities briefly. The sponsor responsibilities, they have to select qualified investigators that take care of this monitoring. They have to monitor the ongoing investigation. See for all you did not remember anything today from my talk, the one thing you have to remember is monitoring, monitoring, monitoring. Monitoring is not optional.

So that's something we always tell. As a sponsor they are responsible for monitoring the clinical investigation. So they have to provide the investigators some of those device kits, device mailings and they have to provide the investigators with all the procedures, like SOPs.

If they do not, you know, submit all of them, how can the investigator follow them? And then maintaining records, so these are some of the, and obviously last but not least the form FDA1572. It is the sponsor responsibility that needs to obtain the 1572 from the investigators.

And next are responsibilities of clinical investigators. And in regulations we have one leader of clinical investigators. There is no PIs. I know constantly people say there is a PA that is, this person is a PA here. But regulations do not define the term. PA is principal investigators. There is only one term, which is clinical investigators.

So we always use the term CIs or clinical investigators. So the clinical investigator obligation is to follow if the sponsor gives them a protocol, the CI has to follow the protocol. Any SOPs or if the sponsor tells them you have to submit a deviation report according to the protocol, then they must do it.

And then also like they have to supervise. I think the supervision is something the CIs have to really keep in mind. Because if there is a problem, if there is a study coordinator or one of the sub investigators doing some study procedures, which is not part of the protocol.

And if the CI did not know, who is ultimately responsible? Who signs the 1572? It is the CI. So who will be held responsible for that? It's the CI. The same way if there is accountability like drug or testing kit accountability, who actually gives out the drug? It is the CI.

So at the end of the day no matter what, they can have so many subordinates doing all sorts of things, but it is the CI who is responsible for any of the conduct, so supervision, supervision, supervision. That's important for the CI. Monitoring is important for the sponsor.

And so what are the common violations we have seen? These are some sponsor violations we have seen. Namely, failed to monitor the investigation or collect information from the investigators.

And also sometimes we have seen cases in inspection where they did not send the deviation reports. The protocol would have required the sponsor to send the deviation reports to the site, to the clinical investigator.

We go and do the inspection and we find that there are no deviation reports, so then the CI still is, oh, no, it's not us, it's the sponsor. So they must, the sponsor, these are the violations we have seen. And also they have to constantly update all the participating sites.

And some of the common clinical investigator violations. Failure to follow protocol requirements and also some of the laboratory testing and confirmatory testing. We have seen cases wherein the clinical investigator would not have done all of the testing, but then there is no source document, there is no case report form.

And then in one case we had to ask the sponsor and then the sponsor then submitted some of the data to the FDA after the fact, when we were starting. I mean, it's, sometimes it could be a mistake, whatever. But I think this is something that must be done. It's a requirement.

And also we have seen cases where incorrect donor samples have been used for testing, which it should not be like this. And then some of the common CI violations are discrepancies between source documents and the case report from, and informed consent.

I mean, as I mentioned earlier, at the end of the day it's the volunteer subjects who sign, who provide the samples, and they sign the informed consent. So the investigator's obligate our regulations strictly tell the investigators to obtain the informed consent. So that's a critical one.

And so how do you evaluate the significance of violations? When we look at the violations, how do we evaluate the significance of that? Do those affect the rights, welfare, and safety of the subjects? Right, at the end of the day they are, we are there to protect their safety and rights. So that's what we want to see. If they are not, then obviously that's a significant one.

And how does it affect the data integrity? Is there any falsification, is there a fraud? Then that's something we do look at. Then we decide whether it is significant or not. And is there a systemic problems with the study?

Suppose if there is a problem with the sponsor and if it is a CRO sometimes we have seen like maybe there are other sites, right? If there is a monitoring with one CRO, the same monitor could have monitored other sites.

Then we want to see how many sites have been affected and what is the nature of this data fraud. Are there other sites that have been affected by it? Then we try to expand the whole thing. And then we will take some actions based on that.

So what are some suggestions for sponsors? So before you start the trial, understand what you are responsible for. So training. This is something again out of the critical component. Training, train the investigators. They have to be trained and train the staff.

And when replacements occur, train the replacements. So that's the next point I do want you guys to bring home. And if you need to talk to the FDA, I have provided some links there. You just have to request a pre-IND meeting and then you can seek advice.

And document all the duties delegated to the contractors so that if they are supposed to do something you can at least tell them, no, no, no, it's not me, it's you. And then before again detailed protocol with all the SOPs and then monitoring.

As I said, monitoring is not optional. So what are the critical activities and is it protocol specific? Then do the monitoring regarding to the right protocol at the right time point. It could be remote monitoring. That's not the problem.

But document all the monitoring and any issues you may have come across. And develop a plan for data collection. Suppose if it is electronic then how are you planning to do that. And are the monitors adequately trained? And then again protocol specific case report forms and don't take too many studies.

We have seen cases wherein the sponsors will have ten different studies. Obviously, you know, they are not able to do their job adequately. And develop a plan for organizing records and also if it is electronic recordkeeping, make sure there is adequate access control so that people who are not supposed to be touching the record will be changing the record. The log-in access. And archival and retrieval procedure. I see there's only ten seconds, but I'm done.

Suggestions for sponsors during, it's like you contact the FDA, the respective FDA product office and ask for some suggestions. And monitoring during the critical activities and then amend the protocol.

Verify that delegated duties are performed. And also keep up with the data as the trial progresses so that you don't have to go later. Try to fix something, okay? If something happens, try to fix it at that time. Don't make it grow bigger, right?

And then train your replacement staff. And after organize the study records so

that because we come and inspect like sometimes for years down the road, the parties may have left, the coordinators, the clinical investigator, but make sure that you organize the records.

And there was a case wherein we went and did the inspection, there was a fire. The sponsor could not find a lot of their records and we asked them do you know what exactly was destroyed in fire and they did not even have an index of records so they couldn't tell us what they lost.

So create an index of the records so that you know. Even if there is a loss, you know what records were lost. Okay, so that's an important one. And this is for fulfilling the retention requirements, which is a regulatory requirement. And also for FDA inspections.

And these are some of the resources I have included in my talk. And please feel free to go, all of those links work, by the way. Okay, so, thank you very much.

DR. LATHROP: Thanks, Bhanu.

MS. KANNAN: Any questions?

DR. LATHROP: Thanks a lot. Additional inspections that are conducted are the pre-market inspections of the facilities. And Nicole Li is going to be reviewing OCBQ's inspection insights and responsibilities for those.

MS. LI: Hi, good afternoon, my name is Nicole Li and I'm a microbiologist in the Division of Manufacturing and Product Quality in the Office of Compliance and Biologics Quality. As you may know, our division conducts CMC or chemistry and manufacturing and controls as well as the current good manufacturing practices or the CGMPs aspect of the review process for CBER regulated products.

Additionally, we also conduct the pre-license and preapproval inspections of manufacturing facilities. And so today's presentation I will be focusing on in vitro diagnostic

devices inspections.

Just as a little bit of introduction to inspections, the agency conducts inspections of regulated facilities to determine a firm's compliance with the necessary requirements and laws and regulations. And those may include the FD& C Act or other related acts.

To determine a firm's compliance with the regulations, CBER will conduct inspections. And so in this presentation today, I will be identifying examples of IVDs that are regulated by CBER and discussing the types of IVD device inspections based upon how these devices are regulated.

And finally we'll conclude with the IVD device inspection process. So my hope is that by the end of today's presentation you'll have a good understanding and the necessary resources to prepare for your next inspection.

So as you may know, CDRH or the Center for Devices and Radiological Health are responsible for most of the medical devices that are under FDA oversight. However, CBER is also responsible for medical devices which are known as the IVDs. And these IVDs would include tests for blood donor screening or other confirmatory clinical laboratory testing.

An example of IVDs that are licensed include the blood donor screening tests which may include the HIV, HTLV, Hepatitis B and C viruses, reagent red blood cells, blood grouping reagents, antihuman globulin, and other approved or cleared IVDs would include diagnostic HIV test kits, automated immunohematology analyzers, plasmapheresis machines, and quality assurance reagents.

So the importance of understanding why we're dividing this distinction, making this distinction between licensed and approved or cleared IVDs is important to understand the types of inspections that can occur.

So we'll begin by discussing the licensed IVD inspections. So the first type of, there are four types of inspections for licensed IVDs. The first inspection would include the pre-license inspection. And this is performed during the CBER managed review process when a biologics license application is submitted.

The second inspection that can occur is the preapproval inspection when there are significant changes that are made to the biologics license application. And this would accompany the reporting of these changes when you submit your prior approval supplement or the PAS.

These two types of inspections are performed by my colleagues in DMPQ. What's important to understand about these first two inspections, the pre-license and preapproval inspections, is that these inspections typically can occur almost immediately when you submit your submission.

However, we will work with the firm to arrange an appropriate time to conduct these inspections and this typically occurs around midcycle. And I'll go into further detail about the inspection process and how the inspections are scheduled.

What's also important about these two types of inspections is that there are instances where these two types of inspections can be waived based upon the firm's compliance history and the nature and the scope of previous inspections. And I refer you to SOPP 8410 for further details.

The third type of inspection that can occur is the surveillance inspection, and this inspection is performed by a special cadre known as Team Biologics in ORA. And what they do is to make sure that the firm is meeting the basic and simple CFR requirements and they're basically understanding if the compliance is, basically make an assessment of the compliance by

the firm. And this typically occurs biennially.

The fourth type of inspection is the for cause or directed inspection. And this inspection is conducted by the ORA investigators and is typically performed with response to specific information that the agency has come across.

And this may be avenues such as complaints, information from former colleagues, or perhaps when the firm is reporting other information of adverse reactions. And this is the most unscripted inspection and can occur at any time.

So we'll move on now to the inspections of approved or cleared devices. And again this also has four types of inspections. The first type of inspection that can occur is a PMA preapproval inspection.

This inspection is performed during the managed review process of the PMA and is performed by ORA. So this inspection basically determines the firm's ability to design and manufacture the device. And typically it occurs during the midcycle.

The second type of inspection is a PMA post-market inspection and is also performed by ORA. It's really the first instance for the agency to evaluate the [product on] market once it's been approved. And this typically occurs after the PMA approval which is generally eight to twelve months.

The third type of inspection is a surveillance inspection which is quite similar to the surveillance inspection for licensed products. It's also performed by ORA and typically occurs biennially for Class II or Class III devices. For all other devices it's performed on a risk-based process for the frequency.

And again, for the for cause and directed inspections, we've discussed that and it occurs similarly like the licensed inspections.

So there are various acts that confer the authority to inspect on the Secretary of the Department of Health and Human Services. Regulations delegate that authority to the Commissioner of the FDA who further delegates that authority to the agency to inspect the facility.

And specifically, Section 351 of the Public Health Service Act and Section 704 of the Federal Food, Drug, and Cosmetic Act provides the regulatory authority to conduct inspections at any establishment where biological products are manufactured.

And for licensed products under 21 CFR, Code of Federal Regulations, 601.20, a biologics license application shall not be issued except upon a determination that the product and the establishment comply with the applicable regulations.

Now we'll move on to discuss the inspection preparation process. Now as I mentioned earlier, the agency can go at any time once it receives your submission to inspect your facility. However, to ensure that the inspectors are able to observe the pertinent manufacturing operations, the agency will reach out and arrange an appropriate time to conduct the inspection.

What we'll request at this time is an in-depth production schedule where you'll identify if there are any issues that may delay the inspection. And these may include things such as the winter or summer shutdowns when you perform your maintenance.

Additionally, during the inspection preparation process we'll discuss logistics. We'll ask you to confirm your address and discuss if there are any special arrival instructions. If you don't want us to go through a certain door, just let us know so we'll tell, you know, our transportation to arrive at a certain entrance.

Additionally, we'll discuss restrictions such as wardrobe, jewelry, cosmetics, and notebooks. Some inspectors may be bringing a hard cover canvas or a cloth type of material

bound notebook. And if your procedures require that fiber releasing notebooks or notebooks that require it to be wiped down are not permitted in your facility, then please let the inspectors know in advance so we can discuss other alternatives to allow the inspectors to take notes.

Additionally, if your facility has any special vaccination or other special requirements, please let the inspectors know in advance so that we can make prior arrangements to obtain these necessary changes or requirements so we meet your facility's requirements.

And lastly, we'll discuss workplace and office support and Internet connectivity that allows the inspectors to operate during the inspection.

During the inspection planning process, we'll also provide a pre-inspection document request list. This list is not, includes procedures and other documentation that may be, that the, sorry, that the inspection team is requesting in advance that you provide prior to the team's arrival. And while it's not an all-inclusive list, it does help you stage your next inspection.

So we'll next discuss the inspection process. So on the first day of the inspection we'll do introductions and we'll present our credentials to the most responsible person. If this is a domestic inspection, we'll issue a form FDA 482 notice of inspection. Also during the introduction meeting we'll discuss and state the objectives of the inspection.

On the first day of the inspection we'll conduct a facility walkthrough, and throughout the rest of the inspection we'll do an observation of production according to your production schedule, a review of documents, and hold discussions with subject matter experts.

CBER fulfills its regulatory obligation to inspect establishments where biological medical device products are manufactured in accordance with the following guides. And I recommend that if you're a facility who's going to be inspected that you review these guides.

And they include the Compliance Program Guidance Manual Inspection of Licensed In Vitro Diagnostic IVD Regulated by CBER, the Guide to Inspections of Quality Systems, and the Investigations Operations Manual.

To ensure that the firm is able to meet the requirements that are specified in 21 CFR Part 820, which are the medical device CGMP regulations, firms can apply a model that includes a seven subsystem approach to the quality system. And the entities of the subsystems include management, design controls, production and process controls, records/documents/change controls, materials controls, facility and equipment controls, and the corrective and preventative actions.

What's important to understand about this model is that these subsystems are not discreet entities where in fact they are interrelated and each subsystem can affect each other.

We'll next move on to the Compliance Program Guidance Manual inspection of licensed IVD diagnostic devices that are regulated by CBER. And these are the types of actions or, that we perform during the inspections. The next few slides will discuss these actions.

And so they include verify all relevant data were submitted to the BLA or supplement and that data is accurate and complete. Verify the device history record is accurate and complete when compared to the submission.

Observe the processes, manufacturing, and testing and compare the description or the DHRs submitted in the CMC section and other sections of the submission. Review process controls, analytical testing, and process validation for the finished device.

Review facility and process changes not covered in the submission that could affect the product or manufacturing. Review design control documentation and compare data if submitted in the application.

Review batches or lots that did not meet and met specifications and verify out of specification investigations are completed. Review data as needed, determined by the submission review for qualification of new manufacturing areas, equipment, and utilities.

And lastly, to verify raw materials and components testing have been performed and verify the new product has been incorporated into all aspects of the quality system. Review the shipping validation for the finished device.

And verify procedures have been established for reporting of biological product deviation reports, BPDRs, and medical device reports, MDRs, per 21 CFR 600.14 and 21 CFR 803, respectively. My two colleagues in OCBQ will be discussing these two topics in the next presentation.

So over the course of the inspection we'll be reviewing documents and conducting discussions with subject matter experts. Now there are instances where significant issues and concerns may be raised and they may be issued on the FDA Form 483.

And these are some examples that were recently issued on inspections. We'll begin with the first example. It states that, and please note that some of the information has been redacted to provide, you know, so we're not releasing important information from the companies for confidentiality.

So the first example is the management and evaluation of unplanned maintenance activities of critical pieces of equipment used in the manufacturing are not adequate. Specifically, quality is not involved in the oversight of unplanned equipment maintenance activities and impact on test results.

There have been no excursions, CAPAs, or change controls initiated from the unplanned equipment maintenance events. There is no evaluation of the equipment repairs as

performed by the service providers to determine if the repair is adequate to prevent repeated equipment failure or that the repair has corrected the cause of the malfunction.

What's important to understand about this example and what it illustrates is that management is really at the core of he quality systems and is linked to all of the other subsystems. Management controls are therefore important to ensure the effectiveness and sustainability of a good quality system.

And so management is therefore ultimately responsible for the quality system. And in this example, management should have ensured that there were adequate resources to, within its quality management system and establish an effective quality management system that allows for monitoring and any necessary changes to be performed.

We'll discuss next about the second example, which stated the design verification results, including the identification of the design, methods, date, and the individuals performing the verification were not documented into the design history file.

In this example, the firm should have properly controlled the design history process by establishing and maintaining procedures that document the design history file, which include the confirmatory results that demonstrate that the design output meets the design input.

For the third example, it stated that the facility design does not contain sufficient space to perform operations related to manufacturing activities as evidenced by: In the sample receipt area, multiple delivery boxes were piled up partially blocking access to a work table and a refrigerator. A freezer in the manufacturing area was used as a benchtop for activities that were related to manufacturing.

In this example, the firm should have established a facility design that provided adequate and appropriate physical environment and equipment to manufacture its product.

This is an example of the fourth observation and it stated procedures to control labeling activities have not been adequately established. For example, 320 labels were issued for manufacture of Lot AA with 305 labels applied to product vials and two labels within the DHR. There is no formal reconciliation process to account for the remaining thirteen labels.

And secondly, the mislabeling of materials led to two instances for potential mix-up as noted in exceptions A and B. In this example, the firm should have established appropriate procedures that should have controlled and monitored its manufacturing processes which included labeling.

And in the final example it stated the control of documents and management of document changes is not adequate. Specifically, the removal of obsolete manufacturing procedures from the area, manufacturing areas is not being performed in a timely manner so as to prevent the use of an incorrect version being followed and has directly led to three excursions.

In this example, the firm should have established appropriate written procedures to control documents which included the removal of obsolete documents and the distribution of approved documents.

Now we'll move on to inspection tips. I understand from, you know, whenever we go out on inspections that inspections can be stressful and can be a daunting process. So hopefully these inspection tips will help you on your next inspection.

The first one includes allowing reasonable access to manufacturing areas, documents, and personnel. So during the inspection the inspection team will identify what area, manufacturing areas it will want to see, what documents it will want to review, and what personnel it may want to talk to.

Secondly, provide documents as requested. We understand that there are a

number of documents we review during the inspection and if there are ever any instances where you anticipate a delay with providing these documents, please let the inspection team know in advance so that we can arrange our inspection schedule appropriately. And if anything, we can perhaps identify another alternative to our previous request.

Now some exceptions of what we will not review is, includes the management reviews, quality audits, and supplier audit reports. But we may review associated procedures and information in the CAPA records.

The next tip includes if an inspector has a question or makes an observation that you don't understand, please ask for clarification. This is to the firm's benefit so that you understand and know how to properly respond to the agency's questions and comments.

The next tip includes providing a thorough and accurate and clear responses to questions. If you don't know an answer to the agency's questions, it's certainly acceptable to tell the inspector that you'll get back to the inspector with the appropriate answer.

And lastly, if you disagree with the inspector, please state your position with supportive information and make sure that the inspector accurately and appropriately captures your position. Understand also the inspector's comments, agree to disagree, and move on.

And lastly, during the device inspection closeout, we'll be conducting mini-closeouts throughout the inspections which may occur daily. During these closeouts we'll be providing a progress report of what has been reviewed and certain items may be considered as discussion items.

These discussion items, while significant, may not rise to the level of a 483 and will not be cited on the 483, but you should certainly understand the context of these items because they may be cited on the next inspection.

And during the final closeout of inspections, if significant concerns or issues are observed they will be issued on the Form 483 with objectionable issues. And this is issued to the most responsible person at the firm.

If a 483 is issued, you have the option as a voluntary annotation program to include on the Form 483 where you're permitted to respond to the issues identified on the 483. And the four options include reported corrected, not verified; corrected and verified; promised to correct; and under consideration.

Now after a device inspection, you'll want to respond to the Form 483 if issued. What we generally tell and encourage firms to do is take the time to thoroughly and completely address the 483 issues so that there's not a lot of back and forth.

Because depending on your review timeline, you may be running up to the final review clock and you certainly want to have enough time to make sure that your responses are accurate and thorough.

And during this process, the inspection team will be preparing the establishment inspection report which is basically a written summary of the inspection. Field management directive 145 or FMD 145 procedure for release of establishment inspection report to the inspected establishment identifies how the EIR will be released to the firm after the conclusion of the inspection.

And at the conclusion of the inspection, the inspection is classified after the review of a 483, if issued, the EIR, and any responses by the establishment to any observations. And this is done to make sure the, to finally close out the inspection.

And the three classifications include no action indicated, voluntary action indicated, and official action indicated. And these are the references I used in my presentation

today, so I encourage everybody for your next inspection to take a look at these references and make sure that your firm is in compliance and follows these guides. That's it, thank you.

DR. LATHROP: Thank you, Nicole. After licensure the FDA continues to have responsibilities on these surveillance of the performance of the device once it's been released into the clinic. And part of that is the biological product deviation reporting and medical device reporting, which will be reviewed now by, first by Sharon O'Callaghan in OCBQ.

MS. O'CALLAGHAN: All right, thank you. So I'm going to cover the biological product deviation reporting for the CBER licensed IVD products. I've been with OCBQ for a long time, since 1990, and I've been managing ever since then. I've been managing the deviation reporting system, which when I started was, I don't know if any of you were around then, but it was the error and accident reporting system.

We changed that in November of 2001 to biological product deviation reporting to focus really on the deviations associated with the products. So I manage the reporting process for not only the licensed nonblood products, but also the blood and blood component products, as well as the 361HCT/P deviation reports as well.

So we're going to get started with the regulation. So under 21 CFR 600.14 is the requirement for reporting biological product deviations by licensed manufacturers. So it says in the name right there of who's responsible for reporting. It's the licensed IVD manufacturers.

We have a guidance document that we published in October of 2006 that's specific to the reporting for licensed manufacturers of biological products other than blood and blood components.

There's another guidance document that was published at the same time that's specific to the blood and blood components. So when you pull up the guidance document, make

sure that you're looking at the right one.

This guidance provides a little bit more information about the regulation, what we intended, and it also provides some examples of reportable events and nonreportable events, too. Now granted these are not all-inclusive lists, but we have, and I'll talk about this in a minute, but we have a flow chart and information on how to ask the right questions to determine whether a deviation is reportable or not.

So we start off with the regulation of what do I report. And you must report any event associated with manufacturing of a licensed biological product if it meets all of the following criteria.

It either represents a deviation from current good manufacturing practices, applicable regulations, or applicable standards that may affect the safety, purity, or potency of that product, or represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product.

You see we took away error and accident and replaced it with some other extra words, so it's not as, you know, culpable. Also it had to occur in your facility or another facility under contract with you and involves distributed biological product.

So that bottom one is key. If you don't have a distributed product, the rest of that doesn't matter as far as reporting goes. Okay.

So this is what I was referring to that's in the guidance document in a nice flow chart, and these are the questions that are asked as part of that flow chart. If you go through that you've got an event, something happens, and you say do I need to report that. Ask these questions and you should be able to get to the answer of whether or not a report is required.

So was the event associated with manufacturing? This is something that

happened in the manufacturing process. Was there a deviation or unexpected event that may affect the safety, purity, or potency of the product? This is probably the hardest question to answer just because there are things that, well, we don't think it will really affect it.

But when you're talking about affecting safety, purity, potency, remember that word may is in there, okay? So you want to err on the side of that there's a potential for affecting the safety, purity, or potency.

Did it occur in your facility or at your contract facility? So where did the event occur. It may not even be under your responsibility for reporting. So you need to identify that.

Did you have control over the product when the deviation occurred? Were you the facility that had control of the product at the time the deviation occurred? And we'll talk a little bit more about that as well. And then again, was the product distributed?

So under 21 CFR 600.3(iii), we define control to mean having responsibility for maintaining the continued safety, purity, and potency and for compliance with applicable product and establishment standards, and for compliance with current good manufacturing practices.

Basically what this means is you're the facility that says, okay, this product is manufactured, all GMP requirements are met, all of our license application information is met, this product has been labeled appropriately, it's suitable for distribution, and can now be distributed. Whoever's making that decision is the facility that has control over the product.

We define distribution in 21 CFR 600.3(hh) to mean that the biological product has left the control of the licensed manufacturer. So you've made that determination that this product is suitable for release, now you send it to somebody else.

Now it's going to depend on who that somebody else is on whether it's considered distributed. If the somebody else is another, a firm that's a distributor under your

license, under your control, it's still not distributed until it leaves that location.

If you're sending it to either the customer directly or to a distributor that's not affiliated with you, once it's out the door it's out of your control and that's considered distributed.

When do I report? You should report biological product deviation as soon as possible but you must report at a date not to exceed forty-five calendar days from the date you acquire information reasonably suggesting that a reportable event has occurred.

Okay, so basically what this means is once you determine you have an event, you know that there's products distributed, you're pretty sure that there's some potential risk that there may be safety, purity, potency may be affected, once you have that information, forty-five days from there is your deadline for reporting it.

Not after you've already completed your investigation or implemented your corrective action. All of that can come later. You need to submit that report when you, you know, forty-five days from the time you basically discover the event.

Any follow-up information that you obtain after the report's been submitted, if you do your investigation and you find out, you know what, there really wasn't a problem here or, yeah, we thought there was but we did some additional testing. It's still a reportable event because the product was out the door at the time you discovered this.

You can submit that information as an addendum to the report. But you still have to submit the report. So don't wait until you complete your investigation to do the, to submit the report.

So if there's contract manufacturing involved, you must establish, maintain, and follow procedures for receiving information from that person on all deviations, complaints, and

adverse events concerning the affected product.

What's important about this is you have to have that communication with your contract manufacturer because if you contract with a facility to perform a manufacturing step and a reportable event occurs at the contractor, the time period starts when your contractor learns of the event, not when the contractor tells you about it.

So if you have testing performed at another facility and they don't follow the procedures for doing the testing and they tell you three months later, oh by the way, we forgot to tell you that we screwed up here and that product's been out the door, has been distributed for two months, that forty-five days starts when that contractor learned of that event, not when they told you.

So that report's going to end up being late. So it's really important to make sure, because that contractor is acting as an extra arm for your manufacturing. You still have control over that contract manufacturing facility.

How do I report? You must report on Form FDA 3486. It's the biological product deviation report form. You can send it to the CBER document control room by mail or electronically. And of course we prefer electronic submissions and in the last two years we've had one report mailed to us. And I know who you are, so if you're here I may find you.

But, yes, so the electronic system is certainly the most efficient way to submit the reports. The, this is the form, this is the first page that, where you'd put in establishment information, tracking numbers, dates occurred, discovered, et cetera.

And then a description of the event and the deviation codes and identifying it as nonblood. The product information page has the lot number, expiration dates, product types, disposition and notification, whether you notified consignees or not.

So all of this information is captured in the electronic submission, the electronic application. This is the screen that you would start with to put in your user account. You have to set up a user account in order to use the system, which is pretty easy.

You just follow the instructions on creating a new account, fill in the information, you'll get a temporary email, a temporary password sent by email. You put that in and then it'll tell you to change your password.

We did institute an additional security feature in March to have your password changed every sixty days instead of ninety days. And there's some other restrictions on what you can use for a password.

So you put your user account in, you would select the first link, the biological product deviation reporting, and then you would get to this page. So when you create an account initially you have to associate your establishment with your account.

So by clicking on that my establishment button right here then you would put in your, the FEI and it would populate with the facility information and tell you, and just check with you to say you are reporting for this particular establishment, are you an authorized representative, and you say yes.

And then once you get to this screen, again, you would, from that drop down list your FEI and the facility name would display there. And then you can go from there to create the report. So that's to create the new report.

If you, once you create a report, after you pass the first page it will automatically save that information. So it'll give you a preconfirmation number. So if you want to go back to that you can click on edit report. Well, you can enter that preconfirmation number here, click on edit report, and get to the report.

Or you could click on unfinished reports and get a list of all the reports that you've created but haven't submitted yet. The only thing that I want to caution you about here is when you, when you're looking for a report that has been created for your facility, this is specific to the user account that was logged in.

So if you entered the report and you want somebody else to look at it and they have a separate user account, which is fine, they wouldn't be able to log into their account and see your report. Unless you give them the preconfirmation number, then another user could enter that preconfirmation number as long as they're associated with the same facility and pull that report up.

Okay. And likewise with the submitted reports, again, you know, you can review those submitted reports that were submitted in the last ninety days. But they are specific to the user that's logged in.

And just to give you a head's up, we are in the process of evaluating another system, another platform. All the same information that's in the report now will be maintained, but there, it's possible that that'll be a different mechanism to actually access the system. So when we will be giving you at least a month or so notice when that change is going to be implemented so that you can be aware of it.

And then the web, I mean the website with all the information you want about biological product deviation reporting is here at this link. And, which works, I checked it. It has the Federal register notice for the regulations for 600.14 and 606.171 is the regulation for the blood and blood component reporting.

It has the links for the form, the instructions for completing the forms. The deviation codes, there's, when you, there's actually two links for the deviation codes. One is for

blood and one's for nonblood. So that's the licensed nonblood biological product deviation codes is where you would look to find the appropriate code.

We use the codes to, for easier to track and trend the events and put them in the same similar buckets. And the human cells and tissue, the HCT/P codes are also listed under nonblood, but they're in the second section of it. So just make sure that you're looking at the right deviation codes when you're selecting those.

And then with the product codes, again, there's two links, one for blood and one for nonblood. Under the nonblood it's categorized by the type of product, so there's a separate list of product codes for the IVD products.

Both of those code lists are updated every October, each fiscal year at the beginning of the fiscal year. So, you know, we sometimes will tweak some of the descriptions of the deviation codes. Sometimes we may add things if we find that there's certain events that are being reported more often.

And then with the product codes we'll add any product codes that have been approved, recently approved. We'll add those to the list. And then this web page also has the guidance documents and we also provide an annual summary report. I'm still working on FY18's, but that should be out maybe within the next month or so.

And that's kind of a good document to look at, what types of events have been reported. We break it out into the different types of manufacturers. Overall with the IVD products in FY18 we received 105 reports. The year before there was 134. So there's not a large number of reports.

The nonblood repots in total we receive anywhere from about 580 to 620 reports. So as opposed to the blood side which we are receiving about forty-five to fifty thousand reports

a year. So you guys aren't doing so bad.

So I think that's all I had. Contact information, if you have any questions about submitting a report, if you're not sure about the electronic report, don't get frustrated and say I'm just going to mail it. Call me, I'll walk you through, all the way through.

Any questions? I'd rather have the question about do we need to submit this than to have you submit a report and then me try to figure out what the heck you did. Because sometimes they're not always real clear. So I'd be happy to discuss events with you and work through whether you need to report it and, you know, hopefully we end up with a no, not today.

So, okay, do I have time for any questions or we want to hold them?

DR. LATHROP: Let's hold them until the end when everybody comes back up.

MS. O'CALLAGHAN: All right, sounds good.

DR. LATHROP: Thanks, Sharon. And finally we're going to hear a discussion of medical device reporting and adverse events by Bima Patel, also from OCBQ.

MS. PATEL: Good afternoon, everyone, my name is Bima Patel. I am a CSO in the Program Surveillance Branch and recently I took over medical device programs at year and a half since I took over this program.

Some of my responsibility includes issuing directed inspection preapproval inspections, handing complaints, handling MDR reports. There are others. But today I'm going to be talking about medical device reporting for in vitro diagnostic devices.

The Federal Food, Drug, and Cosmetic Act Section 519 grants FDA authority to require mandatory MDRs from manufacturers, importers, and device user facilities. The requirements for MDRs are found in 21 CFR Part 803 and it is applicable to both licensed and unlicensed devices. When I say unlicensed devices, these devices are 510(k) clear or PMA

approved.

Under Section 803, manufacturers are required to submit to FDA initial reports of death, serious injury, and malfunction between thirty calendar days of becoming aware of an event. These reports are also known as a thirty-day reports.

Manufacturers are also required to submit to FDA five-day reports, between five working days. This report is required only for the event that requires remedial action to prevent unreasonable risk of substantial harm to public health or when FDA makes written request for this report.

Another report required by manufacturer is the supplemental report. This report is also required within thirty calendar days whenever manufacturer receives information that was not provided in the initial report.

Under Section 803.40 and 803.42, importers are required to report device related death and serious injury to FDATo FDA and the manufacturer. Also malfunction reports to manufacturers within thirty calendar days of becoming aware of an event using FDA Form 3500A.

User facilities are also required to report device-related deaths to FDA and the manufacturer within ten working days using the same form, 3500A. They are also required to report serious injuries to manufacturer within ten working days. If the manufacturer is unknown, then report is sent to the FDA.

Another requirement for user facility is the annual summary of death and serious injury report. That is submitted January 1st for the preceding year using Form FDA 3419. Even though the user facilities are not required to report malfunction, we do encourage voluntary reporting of device problems through the MedWatch report.

Here is a table that summarizes MDR requirements for manufacturers, user facility, and importers. One thing that I have not listed here is the voluntary reporting. We do encourage voluntary reporting by consumers and healthcare providers.

So when would MDR report is not required? It is not required when manufacturer receives erroneous information and a device-related event did not occur. Also when manufacturer determines that the device was manufactured or imported by [correction: another] firm and when this type of report is received by the manufacturer, that report must be forwarded to FDA with a cover letter.

The final rule requires device manufacturers and importer to submit mandatory medical device reports to FDA electronically. And there are two options for submitting electronic reports.

The first one is eSubmitter software. This is for low volume reporter. Allows submission of MDR one at a time. After you complete the, all the fields, it generates electronic version of 3500A which is submitted to FDA using FDA electronic submission gateway known as an ESG.

The second option for submitting MDR report is HL7ICSR. This is for high volume reporting and it allows reports to be submitted in batches. For additional information on electronic submission or MDR, you can visit the website that I listed on the slide.

There are some general instructions that we would like you to keep in mind when submitting MDRs. First one is under Section B-5. Provide all information known about the event including how the device was involved, nature of the problem, required patient treatment, patient's outcome or final condition.

Under Section D we strongly encourage you to include device brand name,

common name, device procode. Device procode is the FDA product classification code that consists of three letters. And it corresponds to device class name.

These procodes are included in the device approval letters, but I want you to note that the device that are licensed under biological license application do not have this procode. And I'll talk more on the next slide.

Under Section G-5, we encourage you to identify the device by entering the premarket application or premarket notification submission number for approved and cleared devices. For IVDs that are licensed under biological license application, we want you to indicate the BLA number under Section G-5.

Here are the recommendations for submitting MDRs for licensed IVDs. So as I mentioned on the previous slide that these devices do not have a procode. We are in the process of assigning a procode to these devices and once we are done with assigning procode we will be posting instruction on the FDA web page on how to submit MDRs for these devices.

But in the interim, you can choose procode that best fit the device from the procode file available on the FDA web. I have listed the web link here. Also include the brand name and the common name of device when submitting MDRs for licensed IVDs.

And again, we strongly recommend that you include BLA number for these devices. If there are any questions about MDR reporting, they can be emailed to MDRPolicy@fda.hhs.gov or you can write to the address that I have listed on this slide.

And here are some helpful resource websites that I have listed where you can find more information on the MDR reporting.

Thank you, are there any questions?

DR. LATHROP: Thank you, Bima. And now I'd like to ask all the speakers

from this last, this current session to come up to the front and we'll take some general questions for everybody. If anyone has any questions, the previous speakers are also still here, I believe, most of them. So you can also ask those questions as well. And submit your questions to the web. I don't know if we have any web questions.

So as we get started, get warmed up, Nicole, I'd like to ask you, you mentioned that under some circumstances that preapproval inspections can be waived based on the history of the manufacturer. Can you expand on that a little bit?

MS. LI: Yes, that's correct. As I previously stated, the preapproval inspections and the pre-license inspections could potentially be waived, and that's determined based on the compliance history. We do look at the nature and the scope of the previous inspections and any similarities or overlap that is occurring in your submission that you are submitting and the previous inspections that were previously performed.

AUDIENCE QUESTION - MR. SORIANO: Hi, I'm Tom Soriano from Diagnostic Oncology Zero. I have a question about the BIMO presentation. There was one item that I thought was a little interesting and I wanted to know if it's an outdated, or observation about older practice.

It relates to insufficiency of informed consent forms. Nowadays the IRBs, whoever governs, gives us the consent form. And they're supposed to be compliant with all the IRB regs. So is that something, those insufficiencies that you find in those consent forms, something that's recent?

MS. KANNAN: No, I think we constantly come across them. It depends on the study. Like they said, some of them could have been from the other products we inspect. So it could be some of the procedures, the protocol procedures might not have been adequately

described or it could be that the subjects might not have consented to the sample collection, right. So these are the inadequacies that we see.

AUDIENCE QUESTION - MR. SORIANO: And so do you direct those to the governing IRB to say, hey, what's up with your consent form review?

MS. KANNAN: Yes ...

AUDIENCE QUESTION - MR. SORIANO: Or do you put the onus on the sponsor of the CRO to go back and complain to the PO.

MS. KANNAN: Actually, for most of the studies it is the clinical investigator who is responsible for obtaining the informed consent from the study subjects. The ...

AUDIENCE QUESTION - MR. SORIANO: Well, but the consent form, the language in the consent form is generated and cleared by the IRB before it's signed off.

MS. KANNAN: It's cleared, yeah, it's cleared by the IRB but, you know, like all the information needs to be in there because it's the investigator who actually obtains. So at the end of the day it is the CI that needs to actually see that everything is there because they submit to the IRB, right? So ...

AUDIENCE QUESTION - MR. SORIANO: Well, but not the consent form. The IRB gives them, the clinical investigator uses the institution's consent form that's been reviewed as part of the protocol review. That's what I'm just trying to understand.

MS. KANNAN: Yeah.

AUDIENCE QUESTION - MR. SORIANO: Because if there's no way to feedback, you guys are upset about this ICF that you see as insufficient, but it went through the IRB, it was signed off, the study was done, now what do we do? Just keep going on in that cycle.

MS. KANNAN: Actually they should do it early on. I mean, getting the informed consent.

AUDIENCE QUESTION - MR. SORIANO: No, I understand that. But you're the one that's determining it's insufficient and it's after the fact.

MS. KANNAN: Yes, it is after the fact so that's when we tell them like going on. I mean, if it is an informed consent violation, then it is a significant violation for us. We have told the investigator, we have sent warning letters for some of the other products. Not vaccines ...

AUDIENCE QUESTION - MR. SORIANO: To the IRB?

MS. KANNAN: Not to the IRB. Like I said, the informed consent is clearly the responsibility of the clinical investigator. So the IRB comes under a different bucket. What the IRB does is they have to review the informed consent but then the IRB is responsible for the operations under 21 CFR 56. There is an operation component for the IRB. So that's how we cite the IRBs. But obtaining the informed consent is still the CI responsibility.

AUDIENCE QUESTION - MR. SORIANO: Yeah, okay.

DR. LATHROP: So I'll ask another question. So, Kori, you were talking about when products come under surveillance from lot release. Could you discuss that in a little bit more detail? How that decision is made?

MR. FRANCIS: Generally the manufacturer submits a supplement to request surveillance. The surveillance is usually granted after we check the manufacturing history, we check the lot release history, we check our records and make a determination based on compliance and how well the manufacturer has been performing over a number of years.

DR. LATHROP: So, Sharon, if you had, go ahead, please ask the question.

AUDIENCE QUESTION: This is a question for Sharon with we heard earlier about the product codes changing. And with the BPDRs, there's product codes. So when you talk about a new system is this new system going to tie into the new product codes as well?

MS. O'CALLAGHAN: That would be nice. But not at this point and I, as Bima was talking about the product codes I should have mentioned that the product codes that are used for deviation reporting, that's the only place that those product codes are used. They were developed based on what was in our, in the RMS BLA system a long time ago.

We had the product name and a product code associated in there. After a while they dropped the product codes, but I maintained that list of product codes associated with those products. So as new products get approved I just find something that's close and then add another product code. So it's kind of, it's only, those codes are only used for BPD reporting.

With this next version of changing the EBPD application, we're not at the point of making significant changes. It's just a matter of changing the way that you get into the system. But looking at the product codes, there is, there's other ways that we should be able to modify that.

What I would rather see is you just pick the name of the product and get rid of product codes altogether. Because that can be, that can be very confusing. And it makes it clear if you just pick the description of the product is a lot easier than trying to sort through codes. But, so that's on the list, but not for a while.

AUDIENCE QUESTION: Just a follow-up question on the surveillance and switching from lot release to surveillance. Are there any general categories of products regulated by CBER that are exempt from that? Or is that an option for, say, blood grouping products? Are there any that are currently on surveillance as opposed to lot release?

MR. FRANCIS: Well, actually, I focus mostly on the IBD products, not the other products.

DR. LATHROP: I think that would be a good question for DBCD tomorrow. They can address that specifically.

AUDIENCE QUESTION: I'll come back with that then.

DR. LATHROP: Okay. And just to circle around with the product codes, we're so excited about getting product codes for adverse event reporting. They're not the same as the import codes, which are like numbers and letters and quite long. Or the BPDR reporting ones which are specific for that.

The product codes we're talking about are standard for IVDs and they're using CDRH all the time. The BLA is not having them as a real outlier for IVDs. And they're used for adverse event reporting very significantly, but also for searching the product databases.

So if you wanted to search, for example, the PMA database or the, well, there's the BLA database in that database section. You can search for different adverse events under product codes if you want to see historically what's been associated with your type of device.

So they apply to a lot of the different device databases and they're bringing it more in line with how those are thought about. Although Peyton will be talking about some of the nuances associated with the product classification database and putting BLAs under them.

But overall we thought this was a really great addition. And there might be a couple of bumps in the road in getting it implemented, but we're prepared to handle that. So any other questions or anything? Otherwise we can take a break. We can reconvene at 2:45.

Anybody who signed up for meeting one on one with DETTD, you can come and see me and I'll give you a card that tells you where and when to go and who you'll be meeting

with. So if you can come and see me during the break, that would be great. Thanks.

(WHEREUPON, a brief break was taken from 2:17 p.m. to 2:45 p.m.)

DR. HOBSON: Can you hear it? Okay. All right, everybody, we're going to go ahead and begin. This is the second session. This is going to go over devices used for screening for infectious diseases in blood and plasma donations. My name is Peyton Hobson, I'm the Deputy Division Director in the Division of Emerging and Transfusion Transmitted Diseases here in CBER.

I'm going to introduce our division really quickly and then turn it over to our three speakers to close out the day. So the Division of Emerging and Transfusion Transmitted Diseases, or DETTD, is a moderately sized division here in CBER. It is led by Dr. Nakhasi. He's the Division Director, I'm his deputy.

It's composed of four branches. The first branch on the right-hand side of the screen is the PRB or the Product Review Branch, which is composed solely of regulatory scientists with their primary role in the review of your regulatory filings.

The remaining three branches in the division are staffed with what's termed researcher regulators. These are scientists who are tasked with doing mission critical regulatory science. The three branches are LBTSEA, that's led by Dr. David Asher. That's the Laboratory of Bacterial and TSE Agents. The LMV or Laboratory of Molecular Virology, which is led by Dr. Indira Hewlett. And then finally the LEP which is the Laboratory of Emerging Pathogens led by Dr. Sanjai Kumar.

These labs are staffed with scientists who are well-versed in all the pathogens that we're tasked with regulating and we draw on their expertise routinely in the review of the your submissions. The division has about fifty-three FTEs. Like I said before, these are composed of

regulatory scientists, researcher reviewers, and laboratory support staff.

So in fiscal year 2018 the division was responsible for the licensure of seven original BLAs and their eighty-five supplements, clearance of two 510(k)s. We reviewed two INDs and had ten Q submissions.

One thing to note that the division is also responsible for are HIV and HTLV diagnostics. Actually, all retroviral diagnostics reside in DETTD, which was four original PMAs and 87 PMA supplements and twenty Q submissions. So that was our workload in 2018.

With regard to the donor screening tests, these span kind of a wide variety of different pathogens. Shown here on this table are all of the pathogens that we screen for to keep the nation's blood supply safe from infectious disease.

The first two are parasitic pathogens, *Babesia* and *T. cruzi*, the cause of Chagas disease. The following agents shown in yellow are viral pathogens. These are HBV, HCV, HIV-1 and -2, HTLV I and II, West Nile virus, Zika virus, and CMV.

And then finally the bacterial pathogen that we are also tasked with evaluating submissions for is the causal agent of syphilis or *Treponema pallidum*. One thing I do want to point out but I'm not going to dwell on is if you notice at the bottom of the screen, CMV and syphilis donor screening assays are regulated as 510(k)s while the remaining assays are all regulated as BLAs.

So what I want to do is give you kind of an understanding of where your devices fit in, in the evaluation of a blood donation for infectious disease. And what I'm going to do is use a mini-pool format here and I'm going to provide a simplified overview of how it works.

I want to point out how your devices play a critical role in protecting the nation's blood supply. So test donations for certain pathogens can be tested in mini-pool format, and this

is going to be for a NAT test shown up here in the box.

So they're screened in mini-pool format and if the units come back as not reactive, those units are released and then used for transfusion purposes. If they're reactive, the mini-pools have to be deconstructed into sub-pools and tested again with the same test.

If they come back as nonreactive, those units can then be released. However, if some of the sub-pools have then tested again reactive, you have to further break that down into an individual donation and test them again. If all of the ID, all of the donations tested in individual format test nonreactive, the units can then be released.

However, if individual donation units test reactive, those units have to be discarded and the donor needs to be notified for follow on supplemental testing. And what I want to point out here is that the submissions that you send into us for review play an important role throughout this process in many steps to protect the nation's blood supply from the introduction of positive units with infectious diseases.

All the way from the testing of mini-pool format all the way down to the supplemental testing and the confirmatory testing done to actually counsel that patient. So the devices that you give us to review play a very critical role.

And I know a lot of people touched on this before and I want to bring it up yet again is that we are going to start using product codes for our BLAs. These product codes have not been assigned yet. You've heard this said now two or three times, but I'll give you a little bit more granularity as to what we're proposing to do with the BLAs.

The BLAs that we review currently do not have product codes associated with them. So we're proposing the use of two product codes. The first one will be a randomly assigned three-letter code for serology tests used to screen donations of blood and plasma. And

then a three-letter code for tests that are used, or nucleic acid tests that are used to screen donations of blood and plasma.

Once we have these product codes assigned, we will inform the appropriate stakeholders of what product code they should use for their devices in writing. The 510(k)s that we review for CMV and syphilis, those product codes exist and they're listed here.

And then finally just for completeness, the PMAs actually have their own product codes for HIV diagnostics and HIV genotyping. They're just listed here. Just to draw your attention to not to use those if you actually have a licensed HIV BLA. We're going to provide you with an appropriate product code in the near future.

So now I want to change gears and talk a little bit about some of the special considerations for donor screening. And this is really what the rest of today is going to be about. The special considerations for study design for our particular devices.

One thing I want to point out is that the benefit risk determination and analysis is not just done to the person being tested, the donor, but also to the impact on the recipient. So a lot of our benefit risk analyses are done for really two purposes. The donor and the recipient as opposed to, you know, your typical IVD which is really just for that single patient.

And this is also important to point out are some of the public health implications for the safety of the blood supply. It's our job to make sure that not only do we prevent transmission of diseases through the U.S. blood supply but also that we maintain, you know, the public's trust that they have in our nation's blood supply.

Finally, you know, one of the things we really have to do is stay on top of emerging threats. So we're constantly scanning and responding to emerging infectious diseases. And this is a perfect example is obviously Zika which came on pretty strong three years ago and

has waned.

But things like Babesia also, which has garnered a lot of our attention as of late. And we have to really give special considerations for many of our first of a kind tests and really strike a balance between first of a kind and its impact on public health need and what kind of performance we would expect out of these devices to make sure that we can get these tests out in an expeditious manner as these agents emerge.

So just quickly focusing on some of the special considerations for study design, obviously our tests are IVDs, but the study designs are a little bit different when you compare them to a traditional IVD.

With that said, you know, the evaluation of sensitivity for donor screening tests are actually done in subjects who have the disease. And this is important because the intended use population are not disease patients, they're actually quite the opposite. They're normal, healthy donors.

So in order for us to get an understanding of that, we actually ask that you target these populations where you would either have a higher incidence or people actually with confirmed presence of the disease.

Our performance expectations are pretty high. And that's for multiple reasons. And that really drives the size of many of our studies and the scope of the testing. For example, just to put it in perspective, HIV donor screening interdicts a little over three hundred positive units every year, and that's out of about ten million donations.

Now we can't actually have you do a study design that size to show the performance, but we do need you to statistically power that study to establish the performance so that we know and you can show that your tests, when put out there in the field, will interdict

those infectious units.

So that is why our study designs are as large as they are. And you're going to hear about this in much more detail over the next three presentations. The first presentation is going to be by Krishna Ketha Mohan. He's going to go over the analytical validation of donor screening.

That's going to be followed by Dr. Babita Mahajan. She's going to go over clinical validation of donor screening devices and that's going to be, and both of those guys are in DETTD. The last talk is going to be by Dr. Brychan Clark and she's from OTAT, and she's going to go over special considerations for the validation of cadaveric claims for the donation of tissues.

So I want to end and just say thank you and thank everybody for this kind of first day at the meeting. And I would urge you to interact with the DET staff in the remaining time at the end, make yourself, you know, available to them, introduce yourself.

And then also I'm putting my contact information up here so you have it. I know many of you guys contact me anyway, so you already have this. But don't hesitate to contact me if something is going on in the review of your submissions or you have a question or something just doesn't you know, you need clarification.

I'm always here to talk to you. That's pretty much what my job is, is to interact with the sponsors and make sure that we can get your submissions through, you know, as painlessly as possible. To really embrace the least burdensome concepts.

I'd also like to hear, I've already heard many times today from many people in industry about some of the very positive interactions you've had with the FDA staff. And I'll let you know within our division I will let those guys know some of the accolades that you've sent

me on behalf of them.

So that really makes me happy to hear that stuff. So I'm going to go ahead and turn this over to our first speaker who is Mohan Ketha, and he's going to be discussing with you analytical validation of donor screening tests. So thank you.

DR. KETHA: Hello. All right, so here we are. One thing about my talk would be you can see that my job is much easier because it's the later part of the day where most of my slides you can jog up your memory and see, oh, I saw the slide somewhere or some part of the information in the earlier presentation.

So I will be presenting an overview of analytical validation of donor screening tests. And I'm Mohan within the Division of Emerging and Transfusion Transmitted Diseases. My presentation outline would involve an overview of analytical validation as to why, when, and what is required of analytical validation.

Second part would involve general requirements for IVD analytical validation. And towards the end I will touch upon specific issues within our division that are required considering review issues for IVDs for infectious disease screening.

So the first part, why, when, and what. So why? Why do we need analytical validation? Of course this is to demonstrate that the manufactured product meets its prescribed requirements for safety and effectiveness.

In other words, this is a process to evaluate all the confounding variables or the potential influencing factors that could affect the outcome of the result and its reliability. The analytical validation could involve both preclinical as well as nonclinical components, and both are being discussed here.

And coming to IVDs that are involved in donor blood screening, the analytical

performance is as critical as clinical performance because of dearth of samples when it comes to donor screening IVDs.

And when do you need to perform an analytical study? In the morning you heard the pre-submission presentation where we constantly encourage manufacturers to approach us with their proposals for studies. And we do get a lot of interaction at this stage mainly for analytical studies.

And at this time when we get the feedback, we expect the manufacturers to come in with all the analytical data before the IND starts in. And definitely when the final submission comes in we require all the analytical data finally included in the final submission.

So what should be included in the analytical validation studies? And this is not a complete, inclusive list, but some of the major salient points that would be covered, such as setting up the blank, setting the cutoff, demonstration of the dynamic range, setting the calibration curve, setting the positive and negative controls.

And also if there's a test algorithm, and many times many of the IVDs have a retest algorithm within the testing flow. So we would like to have a rationale and demonstration of the retest algorithm.

And for quantitative and semi-quantitative assays, we also would like to see the linearity of the assay. And during the analytic validation process, we would also expect the manufacturers to establish, to identify the gray zones of the assay. Because this is very critical to demonstrate whether the assay is predictable enough to give a result for a true positive or a true negative.

And in the performance criteria, we also require analytical validation to include sample and matrix suitability, which includes different analytes.

Most of our requirements come from these guidance and some of the standards that I have listed here. And if you can see, a major part of our requirements are standards, we adhere to the CLSI or the International Committee on Harmonization Guidelines.

So coming to the second part of my talk and these are very general requirements for IVD analytical validation. And this would encompass a series of components. And if I were a manufacturer, I would want my IVD to be precise, to report a result that is precise, a result that is reproducible, and have a very high analytic sensitivity and specificity, and it's not affected by cross reactivity or any interfering factors, and works equally well across the matrix, different matrices, and has a very dynamic range and it's stable according to the intended use claim.

I'll touch upon each of these various components. So coming to the precision and reproducibility. So according to these two studies it is very critical to establish how well the assay yields the same result on repeated determinations. And this is how we look at manufacturer's information on these two studies, precision and reproducibility.

So reproducibility is whenever there's involvement of multiple sites in the testing protocol. And we generally require manufacturers to require a statistically valid approach to evaluate multiple aliquots, multiple lots, and test at multiple sites via multiple runs on multiple days.

And this would enable to differentiate any inter- and intra-assay variability, intra- and inter-lot variability, inter-operator variability, or inter-instrument variability.

Other assay critical or system critical variables such as if an IVD has two plate readers, we would like to see if there's a difference or a consistent performance between the two. And the outcome of all this variability analysis, we expect the statistical results to be expressed as a total variability, which is the percent of, quotient of variation. And by doing this, we know

how precise or how reproducible your IVD is.

So coming to the second part would be establishing the analytical sensitivity. And again, this is a general requirement, so by definition this is the slope of the calibration curve or capacity of a test method to differentiate between two very close concentrations of an analyte.

And this definition is from the CLSI EP17-A2. And within the circles of research between lab and manufacturers, there's a common misnomer between analytical sensitivity. You know the term analytical sensitivity and limit of detection is very easily interchangeably used.

But let me emphasize here, we don't construe analytical sensitivity as equal to limit of detection. They're not the same. So we require both analytical sensitivity to be demonstrated as well as the limit of detection.

So under the analytical sensitivity, the study design may involve end-point, using end-point dilutions such as using a sample that could reflect a high concentration, low concentration, and a negative sample.

And we could even use contrived specimens if there are no standards of panels available. And generally for this study we recommend using three to five concentrations and multiple replicates also recommended to be used in the study.

So what is limit of detection? While analytical sensitivity is the ability to distinguish between two very close concentrations, whereas limit of detection is the ability of the IVD to detect the lowest concentration of an analyte that can be consistently detected, typically in greater than ninety-five percent of samples tested.

And for this, the study design again, we require manufacturers to use known positives or standards of panels if they're available. So we do have some standards and panels as it was mentioned earlier in the presentations.

And use five dilutions per panel. And generally we require a manufacturer test at least twenty replicates per panel and that should include even non-reactives. And finally we require a statistical analysis of this study and that reflects greater than ninety-five percent reactivity.

So how specific is my test going to be? So that's where we want validation to include analytical specificity, interferents testing, and cross reactivity. So this is in other words any cause of significant difference in the test result due to the effect of another component or property of the sample.

As I was mentioning earlier, the variables for an IVD could happen at the sample stage or at the processing stage, at the testing stage, at the instrumentation stage. So at the sample step, these variables could affect the outcome of the result.

And this is where we want manufacturers to test for cross-reactivity or interferents. So cross-reactivity would involve testing other species, serotypes, or genetic variants for the particular organism the manufacturer is claiming the intended use for or cross-reactivity against other disease conditions such as autoimmune disease conditions or infection by other pathogens.

The sample size for these studies are variable for different conditions based on the prevalence or occurrence of the disease. And interferents testing, that's the final part where we want to make sure that there's no interferents, either endogenous or exogenous that exist in the sample that could affect the outcome of the text result.

For endogenous interferents, we usually recommend that samples be included spiked with albumin, bilirubin, hemoglobin, lipid, or immunoglobulins. And for exogenous interferents, we generally look for various drugs or supplements that could interfere with the test

result outcome.

So when an IVD comes generally an intended use has the sample starting material as a whole blood, plasma, or a serum or a combination of these. So when a manufacturer comes in with more than one matrix as a claim for intended use, we expect the manufacturer to perform a matrix comparison between all of the different matrices to show that the test performs equally well between the different matrices.

And we also require the study to include lysed or prepared specimen and compared it with neat or diluted sample. If there's a claim for that. And if there's a processing of the sample using different anticoagulants, even that needs to be compared.

And the last part of the matrix comparison would involve any claims for cadaveric claims, which would involve analytical sensitivity, analytical specificity, and reproducibility. I won't elaborate much on this because the following talk, Brandy will take you in detail on this topic.

The final part of an IVD would be establishing stability. Stability would involve both at the very first step, that is the sample step, and the last part as the kit part.

For the samples, whenever manufacturers submit the submission, they have the package insert or intended use that specifies that the samples be stored at a particular temperature, it could be room temperature, refrigerated, or frozen, neat, pooled, or prepared, that is lysed, or on-board. So for all these conditions if at all there's a claim, we would expect the manufacturer to perform the stability study for these conditions and provide the supporting data.

For the kits we need stability data for the calibrators and controls, and all the studies should be performed real time, which form the basis for the shelf life claims. We also expect the manufacturers to perform open kit on board stability studies if there's a mention or a

claim for open kit use of the, open kit use in the package insert.

Finally, the labeling claims we generally recommend require sponsors to perform the studies, so when they come for the feedback we generally advise them to include at least one test time point beyond the proposed claim for shelf life.

Such as if the sponsor intends to claim a shelf life of twelve months, we would recommend them to include at least a test point beyond twelve month such as thirteen month or fourteen month. And they should have data for that showing that it is stable.

So all these labeling claims are based on data and they're not extrapolated because sometimes we have extrapolated studies, so they're not extrapolated. So they're all based on real time stability data.

Coming to the interesting part which is how we deal with IVDs within the Division of Emerging and Transfusion Transmitted Disease. And looking at the challenges and review issues we face and what are the components that we expect in an application when it comes to Office of Blood.

The type of IVDs that we usually receive within the Office of Blood, they are complex donor screening IVDs that have different final analytes such as antigen, antibody, or nucleic acid. And the technologies could vary right from an ELISA, from a chemiluminescence based assay to a PCR assay and so on.

And the limit of detection parameters could vary from assay to assay. Sometimes for the same organism we may have two different manufacturers who have a different limit of detection pattern, so it's very difficult to analyze what, an LoD from one manufacturer could relate to the LoD of a second manufacturer.

So we do handle all those different complexities of IVDs. And the final part is

the different clinical samples or the starting material that could be involved in an IVD. And that would also determine what would be the sample size for analysis for genetic variants or, and that could entirely depend on the prevalence or the risk of transfusion transmission of that particular organism, pathogen, or disease.

So coming to the very specific concentration and review issues for precision and reproducibility. We generally require advice, manufacturers to include a panel of six to ten well-characterized specimens for this study. And these should represent a clinically relevant range which should include a minimum of one positive and one negative sample near the assay cut off. And this should also include the assay controls and calibrators.

We do have a requirement for different, if there's a different group or a different specimen matrix or a different analyte or a different genotype. We have different group or panel of specimens for each of these varying factors. And we recommend that they use a different set of panel of specimens for each of those different variables.

And all these precision and reproducibility studies should generally be tested using at least three kit lots at three different sites.

Coming to the analytical sensitivity, so this I'll discuss in detail here. As I was touching upon the general concentrations earlier, now these are very specific considerations. For any IVD that comes in for intended use claim for any, each specimen group or genotype or strain, we require testing be included for sample matrix such as serum or plasma.

And the approaches for the sensitivity should include end point dilution using earliest time of reactivity in serially-collected specimens or comparison to reference standards, comparison to an independent method, or using quantitative biochemical characterization.

In the absence of any of these approaches, we also advise manufacturers to use a

direct comparison to an FDA-licensed, approved, or cleared test. And we recommend sponsors to use controls targeted to clinical decision points such as using low positive between, say, one to three signal to cutoff ratio or using low positive that has a one to three x LoD.

And we also require sponsors to validate their assay's gray zone. So it is during this analytical validation of process step at the earlier stage of development that if you could identify the assay's gray zone, that would help in fine tuning by the time you are coming for the main submission.

So part two of analytical sensitivity, this would touch upon using standards or reference panels. We recommend sponsors to use appropriate standards or CBER reference panels. And some of the panels are available.

Earlier it was indicated for HIV, HCV, HBsAg, *Babesia*, and so on. We do have, include seroconversion panels also in this analysis whenever it is available. For example, using multiple specimens from at least ten subjects undergoing seroconversion. I will elaborate more on seroconversion in the following slide.

The third part would be including low titer panels for each strain, analyte, or matrix that is in the intended use claim. And generally we recommend using six to ten specimens per panel. And dilution series, so we recommend having a dilution series, at least ten specimens from ten subjects for each strain or matrix.

We also require manufacturers to use any known positives from relevant populations such as samples from an HIV-1 high risk group. And if at all there's any claim for genotypes or strains in the intended use claim, we require manufacturers to confirm the sequence identity in the analysis.

FDA prepares and provides panels of samples, and as it was mentioned earlier

these are provided free of charge. And we do have different panels for certain analytes. And these analytes are at various concentrations or levels.

And sometimes there could be a discrepancy or a difference between the matrix where the IVD may use and the analytes or panels that are constituted here at CBER, but we do consider that approach.

And analytical sensitivity, when we are using the panels of samples, this should not be confused with lot release panels. These are mainly for validating your analytical sensitivity. These are not for lot release panels. And number of samples that correctly are being detected by the IVD is being evaluated in this analysis.

Ass I was mentioning earlier, we need seroconversion panels. So many a time for IVD donor screening assays there's a dearth of clinical samples and real clinical samples from blood donors with values near the cutoff are rare.

And seroconversion samples are real samples with analytes at relevant clinical concentrations. So it helps that the panels collected from plasmapheresis donors who are in the process of seroconverting, we do have a series of samples and we could quickly identify among the two tests that are being evaluated which one picks up the earlier sample or the earlier time point.

Coming to analytical specificity. For this analysis we require a manufacturer to include samples for any intended use claims for other strains or variants and also to confirm identity if there's a genotype variance.

To include samples that involve other diseases or medical conditions such as autoimmune or infections by other pathogens. And potentially interfering substances such as endogenous or exogenous I had earlier touched upon. And also has different anticoagulants or

collection tubes.

Again, here we are very flexible that we look at the sample size for all this analysis based on the requirement or based on the conditions and this could vary from condition to condition.

And the labeling claims, if there's any interference that is observed in these studies, that comes out in the labeling claim in different studies of cross-reactivity studies.

So finally coming to the submission. So what do you need to submit and what to expect coming from a submission that has analytical data. So the device performance. So the device performance or analytical validation should include summaries of study designs.

And study designs would mean all the materials, procedures, analysis, and oversight, sample collection, selection criteria, handling, and storage. It would also include statistical and clinical consideration.

And it should include all documentation that the whole testing, the entire validations that was performed, at an approved facility using good laboratory practice.

The submission should also include summaries of results and line data for all studies. This is very critical because data for each specimen should be included in that analytical validation summary report.

Each assay run performed including failed runs and documentation and justification of excluded data. And documentation and justifications of deviations, outliers, et cetera. So all these components help us to review how well the assay performed and if there are any outliers.

So what are the common review issues that we usually faced during any of the submissions that come into Division of Emerging Transfusion and Transmitted Diseases? We

see that the results don't meet the pre-specified acceptance criteria.

So we generally want manufacturers to send in an acceptance criteria and double check that the testing is meeting their own specified acceptance criteria. If not, they need to redo those experiments.

And sometimes , because most of the IVDs, blood screening IVDs have a limit of detection, we see a very inconsistent definition of limit of detection, ranging from one study to another study, the limit of detection could vary from study to study, which makes difficult for us to evaluate how sensitive or how reproducible or how specific the assay is.

And sometimes the validation that is submitted in the final submission, we see that the validation was not performed on the final configuration of the device. Including algorithm and cutoff. So what happens is during the development phase of the IVD, there could be some changes.

But what we require the manufacturer is any change, is okay. So you report the change, you come and get the feedback, but all those changes have to be performed and compared to the pre-existing one and perform a bridging study to show that there's an equivalence of performance and the final configuration of the device has been validated. So that your final marketing configuration device is the one that should be validated.

Sometimes insufficient samples are included in the studies which are near the cutoff. So preferably we require statistically justified samples to be included in the study. And very rarely we do see some intended use that are in the IVDs that we have received, the intended use claims are too broad. Such as it just says "for infectious disease testing".

We always look for very specific claims. If it claims for organism X and species Y, we give the intended use labeling claim only for X and Y. And those X and Y have to be

supported by supporting data.

And sometimes IVDs, they do have a broad range of extreme variables in the, their dynamic range and the guard bands that are defined in the validation study do not include the extreme variables. So we require manufacturers, it would be great if they could define the guard band variabilities, extremities, and then perform the validation using those extreme conditions of guard bands.

And as I was mentioning earlier, gray zone should be included in the final device. And how it was resolved so that we know that there are true positive and true negatives based on the real, precise cutoff data.

And sometimes not all claims are being validated in the final submission package, so if we see any claim that has not supported by justification or substantial data, we don't look at the data. Rather, we ask the sponsor to provide supporting data or remove the claim.

All right, so to summarize analytical data, this is the first part. So this is the basic of your studies that where you're coming into FDA, even before the IND. And you're giving us the data to show that the IVD functions well. And these are the foundational studies.

And it would establish your device performance such that we have a confidence to look at your IVD and say that, okay, the final results are very precise and this IVD has a high sensitivity and specificity and the results are reproducible across variables and demonstrates no effect of interferents.

In other words, it would establish a robust performance. These are some of the references that I have highlighted and the blue ones would indicate they are guidelines from CLSI and there's a guidance here.

And again, any questions at any stage of the study and validation, ask FDA.

Approach FDA. We are here and we provide a lot of feedback right at this stage of the validation actually. Thank you.

DR. HOBSON: Thanks, Mohan. Okay, so building on that, up next we have Dr. Babita Mahajan. She's going to give us an overview of the clinical review of donor screening tests. Babita.

DR. MAHAJAN: Good afternoon, everyone. I know everybody's tired. We have just two more to go. So Mohan talked about analytical, establishing the analytical performance of the device. Following analytical performance, the clinical performance of the device is established.

Let's go over the clinical studies that are used to establish the safety and effectiveness of the blood screening devices. During this presentation, I will go over the interactions or the opportunities you have to interact with FDA for clinical study design.

I will go over in details of clinical sensitivity, specificity, and reproducibility studies. And in the end I will touch a little bit when you can use assay migration pathway instead of performing the full clinical studies.

So first going over interactions with FDA for clinical study designs, you have numerous opportunities to talk to us on your study designs. These interactions are meant to be a dynamic process that can happen throughout the product lifecycle.

You can use it while you are at early product development phase, during the licensure process like BLAs is under review, or while you want to upgrade or change your device once it's approved. You can come and talk to us at any time.

These interactions are meant to be beneficial both to FDA and to the sponsors. This is the time we can set expectations and we ensure understandings among each other.

So first in this series could be the INTERACT or informational meetings which happen during the early stage of development. So what I mean is these are informal consults that happens during the device development phase.

As stated earlier, this should be beneficial both to FDA and to the sponsor. As FDA, we can learn about your plans, what new assays, what new technologies are in pipeline, what you are planning to bring to the market.

Sponsor, at your end you can learn about FDA's current thinking at that point of time, what new guidances can affect the decision, or are we seeing any issues related to any specific analyte. There are some new assays coming up, are we seeing some kind of issues with some analytes? We can talk about that.

But the feedback that is provided at this stage, we don't provide written feedback. This is the time for open discussion and the feedback that we provide to you at this stage is not binding, unlike the one which happens during the Pre-sub phase.

So our next interactions would be at the Pre-sub stage, that is, we can also call it the pre-IND phase when your device is ready for clinical trial or validation. This is a good time to come and talk to us about your clinical study protocol, discuss your detection algorithms, and this is especially important that the FDA and the sponsor are on same page if you are developing a new assay for a new analyte.

We can talk about what high risk population could be used and how we are going to define that. We can talk about if the disease is regional, how the regions of endemicity has been stratified, how do you decide that.

We can talk about what gold standard you can be using if there is no licensed or approved assay. We strongly, strongly recommend this interaction, because a well-designed

clinical trial really streamlines the licensure process.

Moving on, our next interactions could be at the IND phase. Caren in morning presentation provided you with the details of IND process which allows the initiation of a clinical investigation.

Reiterating again, it's our expectation that you submit us the complete package. Some of the important components that you ensure that the human subjects are not exposed to any unreasonable risk of injury or illness.

The information that you provide to us is sufficient so that we can assess that what risk and what could be the risk to the subjects. The subjects should be well-informed, like we heard a lot about informed consent.

The clinical investigators should be well-qualified, whoever is taking up this task. We really stress here that we expect a timely response from your side for any additional information that we seek for at the IND phase, because this is a thirty-day review period.

On FDA's end, we will provide you with the decision within thirty days. Along with the decision, we might provide you with some recommendations that can help you with the study design so that the study achieves its goal.

We might point you to some issues which might not be important at IND phase and doesn't affect our IND decision, but that might be important to your future BLA submissions or future applications.

And if your study is put on hold because of some safety reasons, we will provide you with written response with all the hold issues and if there are any non-hold issues, we will inform you about that, too.

Further on, our next interactions would happen once you submit your BLA

license application. This is the time when we will review the clinical data for safety and effectiveness. We will look at your, we will look at in details your clinical study results, the sensitivity, specificity, and reproducibility.

I will go over a little more details onto that. As the clinical protocols are usually agreed upon at the IND phase, we usually don't anticipate any major issues in clinical studies. And whatever minor issue we do see, we do aim to resolve them interactively. And again, we expect that you provide us with timely response whenever we have questions for that.

In case your study is put on hold and you are issued a complete response letter, you can use the submission issue meeting pathway and you can come and talk to FDA to discuss the issues that have been raised in complete response letter.

This is really a twenty-one days review period and you can really use this pathway to talk to us on any issues that have been raised.

Further on, once your device is approved you can still come and talk. There might be times we need interactions post-licensure. This will be when you want to update or change your device. Again, this might need a new IND, so it's a good idea to come and talk to us to discuss the intended use change.

Further, there are times when the sponsors use an assay migration pathway when they transfer an assay that has been approved, licensed, or cleared from an old system to a new system. This again may require a new IND sometimes. And we strongly recommend that you use the pre-submission pathway to come and talk to us about the study design early on.

Now I want to move a little bit towards the important components of clinical study design. Here what our review focuses is if we are reviewing your clinical protocol during IND phase, or we are looking at your data in the BLA phase, that your data and your protocol

should support the intended use which you are claiming.

We all know that all the blood screening devices are qualitative and it should give a reactive and nonreactive results. The claims which you have in your intended use should be supported. If you are, the specimen types you are using, be it serum, plasma, whole blood, whatever your intended use is, we need the data to see that that's supported.

You need to claim the specimen, you need to, the test format that you are using needs to be supported, whether it will be individual test or a pool test. Whatever your claim is, it needs to have the data for that. You need to validate the clinical use, the clinical purpose of your test.

You need, the test needs to be done in the target population. If you are claiming intended use has whole blood donors, source plasma donors, if you are asking claim for cadaveric sample, all these samples needs to be tested. Further on, for blood screening devices, the testing has to be performed at the site of intended use.

Other key component what we look for is that your study design should account for the disease prevalence and endemicity. Say the test you are developing is regional, like for Babesia, the testing should cover different regions of endemicity and will be looked for how you are defining those regions.

If the test, if the disease is national as HIV, the testing should be planned in geographically distinct population. Be sure that you include the high and the low risk population.

Another important component could be seasonality. If the disease is seasonal, are the clinical trials done at the right time? So timing is important there.

Another important component is the testing algorithm. What approved or

licensed test are you using to confirm the reactive results? Or how you are resolving the discrepant result. This is especially important when you are developing an assay for a new analyte when there is no FDA approved or licensed test.

We will look at what test are you using to validate those discrepant results and how you are validating that assay further.

Other key component would be the analyte that you are detecting, whether this is an antigen/antibody immunoassay or is this a nucleic acid test? If it's a nucleic acid test, is it an individual test like ID NAT or it's a mini-pool NAT. Further on, if you are using a mini-pool NAT, which is usually for mini-pool NAT, we will look at your pool deconstruction algorithm.

As Peyton already talked about, the pool deconstruction can be defined as the resolution of reactivity of mini-pool by testing sub-pools which may be original or freshly made, or samples from individual donors that form the mini-pool. Testing of the deconvolution of the mini-pools to individual samples is requirement for all approved NAT assay. If it has a pool claim.

Now I'll go quickly over what common issues what we see during the clinical study design. These are mostly happens when you make changes while the studies are in progress. You might be making a CMC change, a software change, a cutoff change.

If you make these changes, please provide the rationale and justification of that change. Provide the risk analysis and impact analysis that the change you made does not affect the data that you have previously collected.

If you are updating your clinical protocol against that, please provide the redline version because that really eases the review.

Now I'll go into details of each of these studies. First going through clinical

sensitivity study where our review focus is that your assay should detect true positive. We will look at your definition for true positive, how you are defining a true positive.

Is it based on the clinical truth or are you using a best available gold standard. Are you using an FDA approved test or are you using a lab based test if you are developing an assay for new analyte.

Further, an important discussion is on the sample size. What guide sample size is the highest sensitivity requirements for blood screening tests, which is usually more than ninety-nine percent. The precedent from the previously approved or licensed assays can guide us, can guide us and you for what sample size that could be used.

Like for HIV and HCV, we usually see around a thousand samples. For HBV around five hundred samples. And if you are developing an assay for a new analyte, it's a good idea to come and talk to FDA before you submit your IND protocol.

And it's a, we will look that you have tested the high risk population in clinical sensitivity as studies.

Moving on to specificity study, here our review focus is that the assay should detect true negatives. Again, similarly we will look at your definition for true negative. How do you resolve, what is your resolution algorithm when you see false positive? Is there a donor follow-up associated with that? If so, have you provided the protocol for donor follow-up and recipient tracing?

Specificity tests for blood screening devices has to be conducted in setting resembling the intended use post-licensure. By which what I mean is that the sample should be collected from U.S. donor populations in geographically separate donor collection sites and if the disease is regional be sure that you are collecting samples from regions from high, medium, and

low endemicity.

Further on once the samples are collected, they should be tested at the [clarification: donor] blood testing centers. These testings cannot happen at any random health centers or any hospital labs or something. These testing need to happen at the centers that test the blood samples. That is important.

Again, coming to the sample size, the disease prevalence and high specificity requirement of blood screening assays really guide this discussion. And which again the specificity required for blood screening tests is again above ninety-nine percent.

The precedent from the previously licensed assay can serve as a guide. For whole blood donations, we usually see around ten thousand individual specimens or ten thousand pools if you have a claim for pool testing of the maximum pool size.

If you have a claim for source plasma donation, we usually see around a thousand pools at the claimed pool size. If you want to use another sample size and there is a reason or rationale behind it, you can always come and talk to us about that.

Again, if you are developing assay for a new analyte, come talk to us at the pre-IND phase before you even submit your IND.

Mohan in his earlier presentation had gone into details of reproducibility studies. We sometimes see reproducibility studies presented to us in analytical sections. Sometimes it comes in the clinical section.

We accept it at both the places, it doesn't make any difference. The main issue is if you are doing a reproducibility study, be sure that it is done at three sites. And sometimes some sponsors even combine reproducibility and precision studies together, and that is okay, too.

The panel used in reproducibility studies should be formulated in positive

specimen, near, below, and above the LoDs. And these panels should be used to assess all the variabilities, the testing sites, between instrument, days, operators, run, reagent lots. All of these need to show that your assays produce the same result every time it tests the same sample.

The common issues what we see during clinical studies review is some time multiple reagent lots are not used during the clinical studies. The invalid run rate or the data exclusion information provided to us is either incomplete or sometimes this information is not even provided.

So we request you to document the invalid rate or the data exclusion for each study report. Please provide the justification, the criteria and justification for excluding any data. For any reason, if your invalid rate is high, please provide the reason behind it and what you intend to do to lower that invalid rate.

Similarly, for instrument errors, please document that for each study along with the details on the type of errors you see. Depending on if your instrument rate is high, discuss its impact on instrument reliability and how do you intend to address that issue if your errors are high.

Now finally moving to assay migration, this is one of the least burdensome scientific and regulatory pathway for manufacturers to transfer a previously approved or licensed assay with full clinical data from an old system to an unapproved new system.

This may be used to validate transfer of a manual assay to an instrument platform, assay from a semi-automated instrument to a fully automated instrument platform, or assay from one instrument platform to another which might be a new, improved, or it might have a different automation.

So if you intend to use assay migration pathway, please ensure that these things

have not changed. The intended use should not change. The reagent and assay parameters as cutoff should not change. But there can be minor changes like optimizing the incubation time. There can be minor changes that are allowed but the main reagent and the assay parameters should not change.

The assay and the system technologies should not change from the old system to the new system. Additionally, I might want to point out that some assay technologies are really not good candidates for assay migration.

These are the assays with high, relatively high imprecision near the cutoff because what we are comparing is the old machine to a new machine. So if there is imprecision near the cutoff, it is difficult to do that.

Regulatory outcome really depends on if the acceptance criteria are met or not. And significantly higher false positive and false negative read might lead to the migration study failure. The details on study designs for assay migration is available on our guidance, on our 2013 guidance document which also has specifically an appendix for migration studies that needed to be designed for blood screening assays.

And the common issues what we see are when we see is serial migration. You have a system A with full clinical study, you can move to system B using migration pathway. But if you want to move from system B to system C, you can't do it because you didn't do a full clinical study on system B.

So if you want to move to system C, you have to compare it back to system A where you have full clinical studies. So this is where we, I can emphasize it again that we recommend you come and talk to FDA with proposed migration study early in your design phase.

And to recap, the clinical study should demonstrate safety and effectiveness of your device. The clinical data should substantiate the intended use and the package insert. Each study report should discuss implication of data exclusion, deviation, instrument error, and provide you, and provide the impact analysis.

Justification and impact analysis for any changes to the clinical protocol while the study is in progress. I strongly recommend that you use FDA's Q-submission pathway because we all know that course correction is least expensive when used early.

Thank you. And if you have any questions you can always contact us.

DR. HOBSON: Great, thanks Babita. Okay, we have one more presentation today in this session and it's Dr. Brychan Clark from OTAT. And she's going to provide an overview of labeling claims for donor screening tests using cadaveric blood specimens.

DR. CLARK: Good afternoon, I'm Dr. Brychan Clark. I'm from the Division of Human Tissues, Office of Tissues and Advanced Therapies. Today I'm going to be giving you an overview of labeling claims for donor screening tests using cadaveric blood specimens.

First I'll give you background and history going over some important regulations and guidance documents, and then we'll get into our current recommendations for obtaining a labeling claim for donor screening tests using cadaveric specimens.

So in July of 1997 FDA published the Final Rule, "Human Tissues Intended for Transplantation", also known as 21 CFR part 1270. This required donor screening and testing to help prevent the transmission of certain infectious diseases through human tissues and transplantation.

1270.21(d) specifically required donor specimens to be tested for HIV-1 and -2, Hepatitis B and Hepatitis C, using FDA licensed donor screening tests in accordance with

manufacturer's instructions. It also required FDA licensed screening tests labeled for cadaveric specimens that must be used when available.

Cadaveric specimens or blood specimens from non-heart beating donors are metabolically and biochemically different than blood specimens from living donors. Cadaveric blood specimens exhibit higher levels of inhibiting substances such as hemolysis and lipemia when compared to living donors.

And these interfering substances can influence assay performance, which can potentially lead to erroneous test results. Due to these changes that occur postmortem, to obtain the cadaveric labeling claim for a donor screening test, manufacturers need additional studies and validation are needed in order to be able to use these cadaveric blood specimens with their assays.

Recognizing the need for appropriately evaluated and specifically labeled test kits, FDA began issuing letters in 1995 to manufacturers of donor screening tests. And this introduced the subject of expanding the indication for use of blood donor screening tests to include testing of cadaveric blood specimens. And it also suggested a minimum protocol for testing to follow and validate assays.

So this document, this guidance document was published in June of 2000. It's called availability of licensed donor screening tests labeled for use with cadaveric blood specimen. And what it did was it announced availability of two licensed donor screening tests labeled for use with cadaveric postmortem blood specimens.

And in 21 CFR 1270(d), as I mentioned earlier, it specifically stated that cadaveric samples for HIV-1 and -2 and Hepatitis B should be performed using test kits specifically labeled for screening for cadaveric blood specimens. And this document stated that

it basically they had to start using that by January 31st, 2001.

Okay, going back to 1997 at the same time FDA also announced a proposed tiered risk-based approach for regulating all human cells, tissues, and cellular tissue-based products. Also known as HCT/Ps for short.

This was a broader scope including previously unregulated cells and tissues. And it was issued through rulemaking in three parts, known as 21 CFR 1271. And HCT/P establishment registration and listing, which was issued in 2001, and then eligibility determination for donors and human cells tissues, and cellular and tissue-based products was issued in May of 2004.

And then current good tissue practice for HCT/P establishments, inspection, and enforcement was issued in 2004. The entire 21 CFR 1271 became effective May 25, 2005.

And this slide just shows you that 1271, CFR Part 1271, is essentially in six parts. But we work a lot with subpart C, which is donor eligibility. And that includes the testing.

So 1271.80(c) says a donor specimen must be tested using appropriate FDA licensed, approved, or cleared donor screening tests, according to manufacturer's instructions to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents and diseases, also known as RCDADs.

Establishments must also use a test specifically labeled for cadaveric specimens instead of a more generally labeled test when applicable and when available. A more generally labeled test includes tests labeled for screening donors of blood and blood products as well as those specifically labeled for screening of other living donors.

Other living donors include reproductive cells and tissue donors, organ donors, donors of stem cells or hematopoietic progenitor stem cells, and donors of lymphocytes for

infusion and cellular and tissue donors.

So this slide you can see the first three pathogens, HIV-1 and -2, Hep B and Hep C were listed in 21 CFR Part 1270. Then as you can see in the red box here, the next pathogens were added in 21 CFR 1271. And on the left here it tells you the type of tissue donors that are required for which pathogens.

So basically West Nile virus here is required only for living donors. HTLV I and II are required by viable, or donors of viable leukocyte rich tissues, CMV viable leukocyte rich tissue, and chlamydia and neisseria are only required by reproductive donors.

And this slide just lists all of our adequate and appropriate tests. And now we'll get into the recommendations for obtaining a labeling claim for communicable disease donor screening tests using cadaveric blood samples. This is our guidance.

Okay. Our cadaveric donor screen claim guidance was published in 2004. And it was issued in response to blood donor screening test kit manufacturers' request for information on the studies that they needed to perform to modify the indicated use section or labeling claim so that they could adapt their assays to start using cadaveric blood specimens from HCT/P donors.

And what this guidance document has recommendations for is the studies, such as sensitivity, specificity, and reproducibility. Sample size to include, number of test kit lots to use. It deals with plasma dilution issues and how to include hemolyzed specimens, specimen collection times, et cetera.

So let's talk about specificity studies. Recommendations when matched pairs of pre- and postmortem serum or plasma specimens are available for testing from each donor. So this would be when you have a donor and they serve as the cadaveric donor and the living donor.

You know, pre- and postmortem specimens from the same donor.

So clinical specificity. How often a test is negative in non-diseased donors. So you test a minimum of fifty paired specimens, one pre-mortem and one postmortem specimen from each of the same donor and test a minimum of fifty donors.

And then you determine if statistically significant difference exists between pre- and postmortem specimens based on the frequency of false positive results.

Analytical specificity measures a test's ability to exclusively identify a target substance rather than the substance substances, or different substances. And then you determine if a statistically significant difference exists between pre- and postmortem specimens based on the signal strength.

Sensitivity studies, again, recommending when paired matches of pre- and postmortem specimens, serum or plasma specimens, are available from testing of each donor. Again, you would use fifty paired reactive specimens, one pre- and postmortem specimen from the same donor.

And clinical sensitivity measures how tests are positive in diseased donors. Determine if a statistically significant difference exists between pre- and postmortem specimens based on the false negative results.

Analytical sensitivity, ability to test, detect low concentration of a substance. And then you determine if statistically significant difference exists between pre- and postmortem specimens based on the signal strength and end point dilutions of positive specimens.

Now next we're going to get into specificity studies. This is the most common scenario that we see. And this is where you do not have matched pre- and postmortem specimens from the same donor.

So you concurrently test at least fifty different cadaveric, non-heart beating donor postmortem specimens, from at least fifty different donors and an equal number of random living donor specimens. And using the same test kit lots.

And for clinical specificity you determine if statistically significant difference exists between cadaveric and living donors based on the frequency of false positive results.

Analytical specificity you would determine if a statistically significant difference exists between a cadaveric and living donor specimens based on signal strength.

For sensitivity, analytical sensitivity, sorry. Can you hear me? Okay. For analytical sensitivity a minimum of fifty nonreactive cadaveric specimens from fifty different cadaveric donors and an equal number of random living donors using the same test kit lots.

Both types of specimens are spiked with the infectious disease marker, spiked at a potency near the assay cutoff. You would use a minimum of five individual positive sources for the spiking source, or spiking experiment.

Determine if a statistically significant difference exists between the spiked living donor specimens and the spiked cadaveric specimens based on the signal strength.

Reproducibility studies. You'd use a minimum of twenty cadaveric specimens, twenty living donor specimens, spiked to be reactive near the assay's cutoff. Confirmed true positives may be excluded from the study. And our previous speaker's already talked about the importance of how you determine what's a true positive and what's a true negative, and we would want you to define that in your submission.

You would test each submission, or sorry, each specimen individually in six separate runs on six separate days using three different test kit lots. This will give you a total of eighteen data points per specimen.

It is recommend that specimens are tested on six separate days and stored at four degrees Centigrade to avoid repeated freezing and thawing.

Determine if a statistically significant difference exists between the coefficients of variants and cadaveric specimens versus those of living donors. Many sponsors also provide the percent CV within run, between run, between day, between lot, between site, instrument to instrument, and total percent CV.

Within day, within laboratory percent CV if indicated. And instrument lot to lot reproducibility is required for use with blood donor specimens from living donors and is helpful for use with cadaveric blood specimens as well.

Prior to including a cadaveric specimen in any study, assess for plasma dilution. Transfusion or infusion of fluid might dilute plasma and it can make test results unreliable. We recommend that you test a specimen taken from the donor before transfusion or infusion.

If an adequate pre-transfusion or infusion specimen is not available, you may use an appropriate algorithm that's designed to evaluate volumes that were administered in forty-eight hours prior to specimen collection to determine whether plasma dilution is or is not sufficient to affect test results.

In an adult donor, if blood loss is known or suspected, plasma dilution may have occurred, particularly in a setting of transfusion and infusion of more than two thousand mL of blood or colloids in the forty-eight hours prior to death. Or more than two thousand mL of crystalloids within one hour, or any combination thereof prior to the collection of blood specimen.

It's also recommended that you note the time between death and specimen collection. To accurate document test kit performance, the time cadaveric specimens are taken

should incorporate the full time range of points typically encountered during tissue recovery, between zero and twenty-four hours is the usual.

It's also recommended that you include hemolyzed specimens in the cadaveric study because a large percentage of cadaveric specimens are hemolyzed due to postmortem biologic changes that occur and hemolysis can interfere with assay results. We also like it when you tell us or document the degree of hemolysis if possible.

The guidance document recommends collecting information about storage and handling conditions of both living donor specimens and cadaveric donor specimens. In addition to the studies recommended in the guidance, many sponsors also include validation studies of a range of acceptable storage conditions.

Stability studies or cadaveric studies at different temperatures over different time ranges. These tests inform storage and handling conditions that are included in the package insert.

Other key issues for consideration. What is the appropriate sample size? Our guidance document recommends the minimum sample size for each study, but it's up to the manufacturer to determine what the optimal sample size is for their study design.

How many test kit lots to include in the study? We recommend you include at least three test kit lots in all cadaveric studies, but ultimately it's up to the manufacturer to determine based on their study design.

So in summary, obtaining labeling claim for use of cadaveric blood specimens with donor screening kits, our recommendations are in our guidance document. We went over specificity and sensitivity studies, reproducibility studies, assessment for plasma dilution, hemolysis, and storage and handling information.

For sensitivity and specificity, a minimum of fifty cadaveric and fifty living donor specimens. The small number is due to limited availability and least burdensome principle.

For analytic sensitivity, a minimum of five individual positive sources for the spiking experiment, spiked at a potency level near the assay's cutoff. Depending on the requested claims, studies may include fifty cadaveric serum specimens and/or fifty cadaveric EDTA plasma or other anticoagulants.

These may be labeled as fifty cadaveric blood specimens collected in serum collection tubes and/or fifty cadaveric blood specimens collecting in EDTA plasma collection tubes as an example.

Determine if a statistically significant difference exists between cadaveric and living donor specimens.

Reproducibility. A minimum of twenty cadaveric and twenty living donor specimens spiked to be reactive near the assay's cutoffs. Six separate runs, six separate days. Determine if a statistically significant difference exists between percent CV between cadaveric and living donor blood specimens. Include three test kit lots in all studies.

And that's all I have. These are some helpful resources and our contact information.

DR. HOBSON: Great. Thank you, Brandy. So in the interest of time, we're actually right at the 4:05 mark when we actually have one on one meetings with various sponsors. So I'm going to ask all of the sponsors that actually received a card with a time on it to meet with DETT staff to shift it five minutes. So if you were scheduled to meet with us at 4:05, we're going to start that meeting at 4:10. And then at the 4:20 meeting will be at 4:25.

So I want to turn over the microphone to Julia Lathrop to provide some closing

remarks.

DR. LATHROP: Thanks, Peyton. I wanted to thank everybody for coming to this, the first CBER OBRR outreach education workshop we've had in a long time. Come back tomorrow where we'll talk about issues that are specific to DBCD's devices.

One thing we wanted to, well, I want to thank all the speakers from all the different offices and even centers that came today. And to hopefully give you a flavor of the scope of people who are actually involved when you submit a review and it kind of goes off into the DCC and you occasionally hear and get some feedback.

But the scope of people who are actually involved in reviewing the different aspects of the submission, it's very significant. The interactions and communications are going on all the time during the review of your submissions. And we hope to give you a flavor of that.

And we hope to do this again if people are finding it useful. So any feedback, suggestions for other topics we might include, things that you thought maybe we didn't need to include. You can say that, too. But we really welcome your feedback to any of the speakers today at their emails.

Peyton certainly has opened it up to respond to him or you can respond to me. The slides with the contact information, again will be available on the website at the end of July. And my email will be up there as well.

Unfortunately, we don't have time for questions or Q and A like we did for the other sessions, but please, and people on the web and in the room, please feel free to reach out, ask your questions. If we can't answer it we will send it to people who can answer it.

And we really look forward to robust and dynamic communications with everybody. So the one on ones, we have the people who had preregistered, we have the cards up

here if you don't have one already. Otherwise we'll see you again tomorrow morning at 8:30.

Thank you.