FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)

119th Meeting of the

Blood Products Advisory Committee

July 19, 2018

FDA White Oak Campus
Great Room B
10903 New Hampshire Ave.
Silver Spring, MD 20993

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PROCEEDINGS (8:00 a.m.)

Agenda Item: Call to Order and Opening Remarks

Introduction of Committee

DR. CALIENDO: Good morning everybody. I would like to call this meeting of the July 19th, 2018 Blood Products Advisory Committee to order. It is now eight o'clock.

I am Dr. Angie Caliendo. I am the acting chair of this panel. I am a professor and vice chair of the Department of Medicine at Brown. My expertise is in adult infectious diseases and clinical virology.

I note for the record that the members present constitute a quorum as required by 21 CFR Part 14. I would also like to add that the panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the committee will discuss device reclassification of human immunodeficiency virus, point of care, and laboratory-based serological and nucleic acid diagnostic devices.

Before we begin, I would like to ask our distinguished panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position and affiliation.

DR. BAKER: Good morning. My name is Judith Baker. My area of expertise is public health. I am the Public Health Director for the Western States Regional Hemophilia Network and the Pacific Sickle Cell Regional Collaborative. I am based in Los Angeles, California with the Center for Inherited Blood Disorder and UCLA-Division of Pediatric Hematology/Oncology. Thank you.

DR. DEMARIA: Good morning. I am Al DeMaria. Up until last month, I was State Epidemiologist in Massachusetts, the Medical Director at the Bureau of Infectious Disease and Laboratory Sciences. I am currently a medical and laboratory consultant to the Department of Public Health and the CLIA Laboratory Director for the State Public Health Laboratory.

DR. DEVAN: Good morning. I am Michael DeVan. I am Medical Director for Blood Services at Walter Reed National Military Medical Center.

DR. ESCOBAR: Miguel Escobar, a hematologist, professor of medicine and pediatrics at the University of Texas. Director of the Hemophilia and Thrombophilia Center.

DR. LEWIS: Good morning. I am Roger Lewis. I am Professor and Chair in the Department of Emergency Medicine at Harbor-UCLA Medical Center in Los Angeles. My expertise is in clinical trial design and statistics.

MR. REES: Good morning. I am Robert Rees. I am the manager of the New Jersey State Blood Bank Regulatory and Compliance Program. My expertise is in transfusion medicine and public health.

MR. SPRING: Good morning, I am Brad Spring. I am the Vice President of Regulatory Affairs for Becton Dickinson. I am the industry representative. That is probably my area of expertise.

DR. BISHOPRIC: Hi, I am George Bishopric. I am with the University of Miami Department of Pathology. My expertise here is as a person who is celebrating living with HIV for 30 years.

DR. PEEL: Good morning. I am Sheila Peel. I am Chief of Laboratory Diagnostics and Monitoring at the U.S. Military Program, Walter Reed Army Institute of Research. I am the CAP Lab Director for the Army's HIV Reference Lab. My area of expertise is clinical virology with a focus on HIV and STIs.

DR. SCHREIBER: My name is Marty Schreiber. I am from Portland, Oregon. I work at Oregon Health and Science University where I am a Chief of Trauma, Critical Care and Acute Care Surgery. My expertise is in the study of novel blood products.

DR. KAUFMAN: My name is Richard Kaufman. My expertise is in transfusion medicine. I am an associate

professor of pathology at Harvard Med School. I am the Medical Director for the Transfusion Service at the Brigham and Women's Hospital.

DR. ALLEN: My name is James Allen. Trained as a physician, public health and pediatrics. Worked at the Centers for Disease Control and the Office of the Assistant Secretary for Health for more than 20 years. I was a State Health Officer in Arizona. Retired to North Carolina as the President of the American Social Health, now the American Sexual Health Association.

DR. CALIENDO: We have two of our members on the phone. Dr. Jones? He is not on yet. Dr. Adeyemi?

DR. ADEYEMI: Oluwatoyin Adeyemi, infectious diseases at Stroger Cook County Hospital and associate professor of medicine at Rush University here, in Chicago. My expertise is in HIV and aging and viral hepatitis.

DR. CALIENDO: Thank you. If you have not already done so, please sign the attendance sheets that are on the tables by the doors.

LCDR Brian Emery, the Designated Federal Officer for this meeting will make some introductory remarks.

MR. EMERY: Good morning. I am Brian Emery, the Designated Federal Officer for today's July 19th meeting of the Blood Products Advisory Committee.

Mrs. Joanne Lipkind is the Committee Management Specialist. She and Angelica can assist you with any needs you have at the tables located in the hall. My director, Dr. Prabhakara Atreya, can also help with any problems that you may have.

I would like to welcome all of you to day two of the 119th meeting of the advisory committee held in the FDA White Oak Great Room.

Dr. Angie Caliendo is the acting Blood Products Advisory Committee chair for today. The CBER press media contact is Ms. Megan McSeveney, who is I believe in the audience. Chanda Chhay is our transcriber.

I would like to request that everyone please check your cell phones and pagers to make sure they are turned off or in the silent mode. Please also remember to speak directly into the microphone at all times and please identify yourself. It is helpful for the public, people attending by webcast, and the transcriber.

For the members around the table and the audience, coffee, drinks, and snacks are out of the doors and to the right, located at the kiosk. Members' lunches will be brought to the back of the kiosk – actually, the lunches will be brought to the room in the back behind here, but I will let you know that at lunch time, right

before the break for lunch. These lunches must be purchased ahead of time at the kiosk though.

There are restrooms out the doors and to the right at the end of the hall.

All committee topic discussion needs to be done in the public forum and not in groups during breaks. The FDA and public need your advice, thoughts, and expertise.

The public and industry must stay behind the stanchions and in the audience area. Please do not enter into the FDA or BPAC committee table area. Please wait until the open public hearing designated time to make any remarks using the center aisle microphone when invited by the chair.

Now, I would like to read into the public record the conflict of interest statement for this meeting.

Agenda Item: Conflict of Interest Statement

MR. EMERY: Good morning everyone. I am Lieutenant Commander Brian Emery, the Designated Federal Officer for this Blood Products Advisory Committee meeting at the Center for Biologics Evaluation and Research. FDA and I welcome you to the second day of the 119th meeting of the Blood Products Advisory Committee being convened by the Food and Drug Administration under the authority of the Federal Advisory Committee Act of 1972.

This meeting is open to the public in its entirety. All members and consultants are participating in person.

Today, in the open session, the committee will discuss Topic II, the device reclassification from Class III to Class II of nucleic acid and serology-based point of care and laboratory-based in vitro diagnostic devices indicated for use as aids in the diagnosis of Human Immunodeficiency Virus infection.

The following information on the status of this advisory committee’s compliance with federal ethics and conflict of interest laws, including but not limited to 18 U.S. Code 208, is being provided to participants at this meeting and to the public. This conflict of interest statement will be available for public viewing at the registration table.

With the exception of the industry representatives, all participants of the committee are either special government employees or regular federal government employees from other agencies and are subject to the federal conflict of interest laws and regulations.

Related to the discussion topics at this meeting, all members and consultants of this committee have been screened for potential financial conflict of interest of their own as well as those imputed to them, including those

of their spouse or minor children and, for the purposes of 18 U.S. Code 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts and grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

FDA has determined that all members of the advisory committee are in compliance with the federal ethics and conflict of interest laws under 18 U.S. Code 208.

Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the Agency's need for a particular individual service outweighs his or her potential financial conflict of interest. However, based on today's agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 U.S. Code 208.

Dr. Angela Caliendo is serving as the acting chairperson, Topic II, for the July 19th, 2018 committee meeting. She is an appointed special government employee and serves as a temporary voting member. Her financial interests were screened and cleared prior to participation in this meeting.

Dr. Brad Spring is currently serving as a temporary non-voting member and industry representative to this committee. Brad Spring serves as the Vice President of Regulatory Affairs at Becton Dickinson.

Industry representatives are not appointed special government employees. Hence, they are not voting members and they do not participate in closed sessions.

Dr. George Bishopric is currently serving as a temporary voting member and temporary patient representative for this meeting. He is employed by the University of Miami and is an associate professor of pathology. Dr. Bishopric is appointed as a special government employee; and therefore, is screened for financial conflicts of interest and cleared prior to his participation.

Dr. Judith Baker is a voting member and is serving as a consumer representative for Topic II during this meeting. She is employed by Western States Regional Hemophilia Network in policy. Dr. Baker is appointed as a special government employee; and therefore, is screened for her financial conflicts of interest and cleared prior to her participation.

At this meeting, there may be invited regular industry speakers and other outside organization speakers making presentations. These speakers may have financial

interests associated with their employer or with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflict of interest.

FDA encourages all other participants to advise the committee of any financial relationships that you may have with any firms, its products, and if known, its direct competitors. We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda, but for which an FDA participant has a personal or imputed financial interest that participants need to exclude themselves from such involvement. Their exclusion will be noted for the record.

Additionally, I would like to provide the following specific guidance regarding today's meeting on July 19th, 2018. Topic II of this meeting is determined to be a particular matter of general applicability and as such, does not focus this discussion on any particular product, but instead focuses on the classes of products under discussion.

Presenters and speakers may provide data on products, if any, that will serve only as examples for the committee to have a scientific discussion.

Please note that this BPAC meeting is not being convened to recommend any action against or approval for any specific product. This BPAC meeting is not being convened to make specific recommendations that may potentially impact any specific party, entity, individual, or firm in a unique way. Any discussion of individual products will be only to serve as an example of the product class.

This meeting of the BPAC does not involve the approval or disapproval, labeling requirements, post-marketing requirements, or related issues regarding the legal status of any specific products.

This concludes my reading of the Conflicts of Interest statement for the public record. At this time, I would like to thank you all for your participation. I now hand this back to Dr. Angela Caliendo.

DR. CALIENDO: Thank you. Susan, do you want to introduce yourself?

DR. LEITMAN: Susan Leitman. Clinical Center NIH.

DR. CALIENDO: Okay. We are going to get started. Our first speaker is Peyton Hobson. He will be giving us an introduction to the topic.

Agenda Item: TOPIC II: Device Reclassification of Human Immunodeficiency Virus (HIV) Point of Care and Laboratory-Based Serological and Nucleic Acid Diagnostic and Supplemental Devices

Agenda Item: Welcome and Introduction to the Topic

DR. HOBSON: Good morning everybody. My name is Peyton Hobson. I am in the Division of Emerging and Transfusion-Transmitted Diseases. I would like to thank the advisory committee and Dr. Caliendo for their participation today.

The goal of this is just to really set the stage of what we are going to talk about at our meeting today. The whole purpose of this meeting is to talk about the reclassification of HIV serology and NAT point of care and lab-based diagnostic and supplemental tests from Class III to Class II.

You will notice it is a little bit of a change from the meeting in March. We have actually included supplemental tests in the discussion for today.

What are not included though are HIV assays for blood donor screening, for home use, for viral load monitoring, or for phenotypic drug resistance testing. Those are not for discussion for today.

Before I get to the question that is going to be before the committee, there are two points that I would like to stress. The reclassification process depends on the ability to mitigate risks to health through the ability to generate special controls. Special controls are published as part of the new regulation and they define what is necessary to develop a safe and effective new diagnostic or supplemental device.

Later today, we will ask the committee to discuss in this context do the committee members believe that special controls as described, in addition to general controls, are sufficient to mitigate the risks to health presented by reclassification of HIV serology and NAT point of care and laboratory-based diagnostic and supplemental tests?

Following my brief kind of introduction here, we are going to hear two presentations to give us some background. The first is from Dr. Owen from CDC. She is going to provide kind of a historical perspective and the future prospects. Following her, Dr. David Hardy from Whitman-Walker is going to talk about the clinical application of HIV testing technology and how they are used in at-risk communities.

After those two presentations, you are going to hear a series of presentations from the Agency. Dr. Julia

Lathrop is going to provide the overview of device classification so that the committee is aware of how devices are classified or reclassified by the Agency. That is followed by the current status of HIV diagnostic devices. That is going to be presented by Dr. Anne Eder. Finally, Julia Lathrop will return to give an overview of the proposed special controls that we think can mitigate the risks of potential reclassification.

That is followed by the open public hearing. Finally, I will return and post the question to the committee one final time and turn it over to Dr. Caliendo for discussion.

With that, I would just like to acknowledge everybody within the Division and then across the other centers, too, that actually helped – this was actually part of a two-day meeting for reclassification of multiple devices, including HCV. We got snowed out. That is why we are here today.

It was a big effort. I would like to acknowledge all of the people who were involved with it. There are probably some names we left off the list. With that said, I would like to say thank you, again, to the committee. I would like to ask Michelle Owen to go ahead and provide her presentation. Thank you.

Agenda Item: HIV Diagnosis: A Review of the Past and Prospects for the Future

DR. OWEN: Good morning everyone. I appreciate FDA asking me to come to speak at this advisory committee meeting.

I have no conflicts of interest. As you can see, there are disclaimers up on the slide. I am a federal employee, so those disclaimers have to be there. We are not endorsing any products.

I am going to talk a lot about history, but I am going to actually start with a highlight of why this is important and the need related to HIV diagnostics.

This is a slide that comes from CDC that I am sure many of you have seen before. Basically, it is just showing that we still have people to diagnose. We also definitely have additional work to do to keep people in care and to have viral suppression. We know that viral suppression for HIV is very important.

Obviously, the diagnosis part is highlight in the first bar. Hopefully, by the end of the talk you will see that, actually, diagnostics and diagnostic testing also plays a role in the other parts of this care continuum for HIV.

This is also just a little bit to show you that there are still delays in diagnosing people. This is work

from CDC. Basically, it shows that a lot of people – there is still a significant delay from the time that they are actually infected with HIV and when they are diagnosed. It does seem to vary between risk group and between race and ethnicity.

These first two slides, like I said, were just to highlight the need for continued improvement in both technology and processes for diagnosing people with HIV.

Now, I am actually going to come to the history part. I am not going to go through every one of these individual advances that happened. I have them in the slides so people have all of the history and know what has happened.

I want to actually talk a little bit about the technology. It is somewhat highlighted on the slides here as we go along.

Obviously, the first test that came along was a viral lysate EIA. In that particular test, basically, viral antigens from the virus were on plates. You detected using the antibodies and then an anti-human antibody. Basically, there were some issues with specificity because there was cross-reactivity in human proteins that are actually in the viral particle.

The second test that was actually FDA approved was the Western Blot, which is the second little picture

that is shown there on the slide. Once again, it was to increase specificity because you are actually looking at the individual viral proteins on a piece of paper and, once again, detecting IgG with anti-human labeled products.

To improve upon the specificity of the test, the next test that came along was basically tests to use recombinant proteins and/or peptides. The purpose of this was to eliminate the human proteins that were in the viral lysate and to basically improve specificity.

As we move along, the next real advance came along in 1992 when we realized that we could actually do things a little differently and have a sandwich. That is what this kind of crazy picture is at the bottom right of the slide. The whole idea here is that you can actually change the sandwich format. You can actually detect not only IgG, but IgM. That will be important. I will talk a little bit more about the evolution of what happens when people are infected with HIV in a minute.

The next huge advance that came along was in 1996. At this time, even though it is not part of the question, HIV viral load test came to the market. We could actually look at how people were suppressing virus on therapy.

In these tests, basically, PCR was used with a standard curve. You could actually determine the amount of

virus that was in someone's blood after they were being treated. It was a way to monitor.

The next item that really happened that changed diagnostics quite significantly was the Rapid test came to the market and FDA approved. In these particular tests, it is the second line there. It is actually a lateral flow format in which you can actually detect quickly in a single-use device.

The additional thing that happened with Rapid testing was that there was a different format. It was called immunoconcentration. That is what is actually on the next little picture, the third little bullet there with all of the colors. Basically, what you were showing there is that you could use peptides and/or recombinant proteins and you could detect not only HIV-1, but HIV-2.

By this time, we knew that HIV-2 had made it to the U.S. and tests were approved to detect HIV-2 in this Rapid format.

I realize I am moving quickly. Like I said, I am not showing all of the individual advances that happened.

The next advance that happened really was in 2006. Multiple things happened in this year. One was CDC actually released new recommendations about testing for HIV in clinical settings. I included this not because it was a technological advance, but it was important because we were

trying to normalize HIV testing and the fact that everyone really should be tested for HIV at least once.

Those guidelines were published in 2006 by Dr. Bernie Branson, who I believe is in the audience today. I think you might hear from him later.

The other thing that happened at this time is the first and now only HIV nucleic acid test for diagnostic use was FDA approved. This particular test is not PCR, unlike the viral load test. It is actually something called transcription-mediated amplification or TMA.

It remains to this day the only diagnostic NAT on the market.

The next advance that I want to talk about was something that actually occurred in 2010 here, in the U.S. It actually occurred previously outside the U.S. That was that we could now detect not only antibody to HIV, but also antigens. So the actual P24 capsid part of the protein we could detect.

These were considered combo tests. The first one was approved in the U.S. in 2010.

The other things that continue to happen is that we had CLIA waiver of Rapid tests, these lateral flow tests. Basically, people in the field could get almost immediate results, within 20 minutes or so. Now, we actually have tests that can be completed in about a minute

and a half, once again, to get results back to people quickly.

That is basically what is shown in the upper right. Once again, the Rapid test that now has added antigens. So, there is actually a test that can detect both antigen and antibody to HIV.

These tests, the antigen-antibody test, Rapid test, after it was approved, about a year later, then it actually received the CLIA waiver.

The next significant thing that I would like to say that happened that was not test-related was in 2014 CDC finally revised the laboratory testing recommendations for HIV as far as how people should be tested for HIV in the laboratory. I will talk more about that specifically in the next few slides.

In that algorithm that CDC published in 2014, we moved away from the Western Blot for reasons that you will see in a few minutes why that happened. We started to use a test that could differentiate between HIV-1 and HIV-2.

The original test that was used in that algorithm was the one I showed you on the previous slide that had the spots that you could detect HIV-1 and HIV-2 antibody. That test was removed from the market. A new test came to the market that used something called the Dual Path platform.

That is what is shown in the last little picture on this slide. In this particular case, it is still a lateral flow test, but you actually have things flowing in two different directions. You have the sample flowing in one direction and reagents flowing in the other with the idea that it would increase sensitivity. You can also see more antigens – detection of reactivity to more antigens using that process.

The other thing that happened in 2014 that I think is of significance is CDC also – once again, not related to diagnostic technology, but impacted by diagnostic technology – was the guidelines for pre-exposure prophylaxis for HIV were actually issued by CDC in 2014. They were recently revised.

I will say in 2017 we made a slight revision to the HIV diagnostic testing algorithm based on the fact that there was a little more data with the Rapid antigen/antibody test. That it could be used in the algorithm in certain situations. Still prefer to do laboratory testing if possible, but there were certainly situations where labs didn't have the ability to bring in the large platforms for antigen/antibody combinations.

Now, here we are, 2018. We are at this advisory committee meeting on HIV test down-classification.

So, I alluded to this before. It is a slide that I know many people in the audience have seen before. It is important. It plays a role in the guidelines the CDC developed and also the way people are tested and when certain markers occur.

Basically, this is just a graph showing the response after someone is infected with HIV and the markers that you can detect. RNA is the first marker that can be detected in individuals that are infected with HIV followed by HIV p24, which is the antigen, the capsid part of the virus. That reactivity, while p24 doesn't necessarily actually go away, the reactivity to it does wane as far as being able to detect it. It is because of complexes between the antibodies that the person makes and the antigen.

The next marker that can be detected is IgM. This is not anything new for HIV. Pretty much with all diseases IgM is the first class that is detected in the serum or plasma. After a while, the reactivity switches to IgG.

So, the test based on this performance – we know that markers came along at different times – CDC and my laboratory a long time ago now, about 2006, we started looking at HIV tests to determine when they became

reactive. It was because of the knowledge we had of when the markers occurred in people.

So, this slide is an old slide now. Really, I have more data that is up to date and rearranged in a slightly different way that you will see in a few minutes. Basically, at the time when this work was started, the Western Blot was the gold standard for the supplemental test for diagnosing HIV.

At CDC, we spent a considerable amount of time looking at test performance and when tests become reactive, all of the FDA approved tests that were on the market. As you can see, you work backwards. Western Blot actually was the gold standard so we worked from that. We went backwards.

As you can see from this slide, most of the single-use point of care tests actually become reactive closer to Western Blot compared to the laboratory tests that detect IgG. Western Blot, point of care, IgG test, which I will make a disclaimer about that.

There are several of these tests that we thought originally only detected IgG. There is some evidence now that they actually do detect IgM. The data on this slide, particularly for this test, was the older version of the test. I just want to make that clear.

As you move this way, you start to have tests that definitely detect IgM. These were the lab-based tests that detected IgM and IgG. This is the Rapid test that detects both antigen and antibody. Over here are the tests that – the laboratory tests, at least most of them that are on the market now that detect both antigen and antibody. Not surprisingly, the nucleic acid test is to the far left of the graph. It detects infection closer to the time of infection.

Once again, this was a cumulative frequency analysis. You can kind of think of it as like an IC50 for when diagnostic test becomes reactive. It is not an absolute day. That is a misconception that happens with this slide a lot. I want to make sure that people understand this. These are not exact days. Like I said, you can think of it as an IC50 of when the tests become reactive.

I will say that the order of the test doesn’t seem to change. So, for example, the nucleic acid test always detects closer to the time of infection followed by the antigen/antibody combo test, the IgG only test, and, in general, the Rapid test.

Because we had all of this data, CDC wanted to update the algorithm. In this slide, it basically shows you that the first diagnostic algorithm that was published

by CDC was in 1989. There was a slight revision in 1992 to include detection of HIV-2. Really nothing happened between 1992 and really 2014 when the new algorithm was published by CDC in conjunction with APHL.

This was primarily done because of the evolution of diagnostic technology and the fact that we had tests out there that could easily differentiate between HIV-1 and HIV-2. Prior to the new algorithm, diagnosis of HIV-2 was somewhat challenging. You actually had reactivity on the HIV-1 Western Blot. It often time required some special nucleic acid testing to make that determination.

The algorithm was updated in 2014. Like I said, in 2017, we had a small technical update to say that the antigen/antibody combo point of care test could be used in the algorithm if you are using plasma. That is an important distinction because we do have evidence that with this test it is slightly more sensitive using plasma than whole blood, probably because of the dilution factor, but we can’t say that for sure.

What were the objectives of the 2014 algorithm? It was to improve diagnosis of HIV acute infection. Once again, we had tests that could detect p24 antigen. Hopefully improve and have more accurate diagnosis of HIV-2. As I mentioned, before this algorithm people sometimes that were infected with HIV-2 were misdiagnosed as HIV-1

because of their cross-reactivity on the HIV-1 Western Blot.

We hoped to decrease turnaround time because of the new technology. We hoped that there would be no substantial change in the cost for testing when we did the algorithm.

So this is the algorithm in its current form. The recommendations basically say that you should start in the laboratory with an HIV-1 antigen/antibody combo immunoassay. If it is nonreactive, basically you can stop. However, if a clinician has an indication of an acute HIV infection because of symptoms or because of history, it certainly makes sense to do a nucleic acid test. However, without having that clinical knowledge, the algorithm would stop.

In contrast, if there is reactivity with the antigen/antibody combo test, then you go to an HIV-1/-2 antibody differentiation assay. At the moment, there is only one on the market.

Based on the results from that differentiation test, you have the ability to have HIV-1 antibodies detected, HIV-2 detected. You could have both detected, so it is not differentiated at that point. You can also have indeterminate results for now HIV-1 or HIV-2, in which case the recommendation would be to go to nucleic acid testing.

Primarily for HIV-1 or now if you have HIV-2 indeterminate, it is actually kind of an area that creates some issues. There are no HIV-2 FDA-approved NAT tests. There have been several that have been developed in multiple labs around the country, both at CDC, Walter – at Sheila's lab, also in New York State and Washington State.

So, this is the current algorithm that is recommended by the CDC. However, you will see near the end of the presentation that we realize that there are some holes and it might need to be revised again. We are already starting to work to collect data.

Like I said, the old data about time to reactivity was anchored at Western Blot. Now that Western Blot is no longer the primary means of supplemental tests for confirming HIV infection, CDC kept getting questions about how do these tests line up if you started from the other direction with RNA.

Basically, we did a study where we wanted to show time from reactivity for RNA. Basically, we came up with an inter-test reactivity interval. The hope was by presenting the data in this way it would be valuable to testing providers for interpreting negative HIV test results and counseling individuals on when to retest after exposure.

This is a very crazy, complicated slide. Basically, what we did is we took the data that we had used before from the 50 percent cumulative frequency analysis. We also added data that had been published for the eclipse period.

I should define eclipse in case people don't know. Basically, the eclipse period is the time after someone is infected, but nothing is detectable. That is the eclipse period.

There is quite a bit of data that – not quite a bit. There is some data that has been published from blood donors, et cetera, where they have followed up blood donors to collect data. The data were actually done in a very statistical model that I honestly cannot explain. If you need to know the model, I can get you the person who developed the model.

Basically, what happened is they modeled the eclipse period and then they took the data that we had from all of the other test performance to come up with these test intervals for when someone is – theoretically can be detected using the various technologies, starting from the time of infection. That is basically what this slide is showing.

Once again, not surprisingly, RNA is the first marker that can be detected. The median time was about

11.5 days. As you can see, we have the 25th and the 75th percentiles, which is up here. That is why it gets really crazy. We also go out to the longest interval, which is 97. It is like 33 days. This is actually a representation of that. Obviously, most people the RNA becomes positive long before 33 days. This is the tail.

The next - once again, not surprisingly, the next tests that become reactive are the antigen/antibody tests. From time from infection, it was calculated to be 17.8 days for the median. Once again, next, the IgM test, 23 days. The IgG test, 33.4.

Really nothing changed. In this case, it is not represented by individual tests. We actually have the data from the individual tests. What I can tell you is the order did not change at all from what I showed you on the 50 percent cumulative frequency analysis, which is somewhat comforting. We did the analysis two totally different ways and basically got the same answer.

So, what was the impact of the laboratory algorithm? We do have a fair amount of data now that if someone actually has antibodies to HIV, the turnaround time for individual getting test results has greatly decreased. For example, there is quite a few studies quoted here at the bottom. I will just give you a couple of examples.

In the State of Florida, for example, prior to the new algorithm, about 22 percent of the people would get their results in about two to three days. After the algorithm was published, that went up significantly to like in the 90 percents. All of a sudden, people can get their results back if they have antibodies truly within two days.

It wasn't just in Florida. That also happened in a couple of other places as well. If people have antibodies, the new algorithm really can get people's results back quickly.

It also happened in Milwaukee. They presented at the HIV Diagnostics conference. They were very proud. It wasn't two days. It was 23 hours and like 40 minutes. It was less than two days.

The point being if people have antibodies, they can get their tests back quickly.

There are acute infections identified. We have seen several studies where we do know that we can detect acute infections using the new algorithm. Unfortunately, to do the final confirmation of the acute infection, we need nucleic acid testing.

This is where the algorithm kind of has an issue. That is that the turnaround time is not optimal for any of the NAT testing. The best case we have seen – studies in San Francisco, where they actually went out and verified

off-label use of viral load test, the median turnaround time was around three days for nucleic acid testing.

However, in all of the cases where people seem to be using the FDA-approved diagnostic test, about the best we get is about five to seven days. CDC partnered with APHL to do a demonstration project for public health labs. A lot of public health labs couldn't afford to bring in the nucleic acid test.

In that particular study, we were able to get a result in 10 days with samples – from the time the sample was collected until the actual NAT result was generated with various states sending samples to these reference centers. However, that 10 days didn't mean it got back to the individual in 10 days. We just had the result in 10 days.

Obviously, that is not optimal. People in the HIV – that are acutely infected have high viral loads and have a greater ability to transmit the virus.

The other thing that we did show with the algorithm is that HIV-2 can be diagnosed at the second step of the algorithm. In general, it works better than with the Western Blot.

The cost is an interesting thing. That was another one of the goals. The cost is variable. Some of that depends on who is buying the test, how many tests they

are buying, et cetera. There is a whole host of factors related to that.

In general, like in Massachusetts, they concluded when they went to the algorithm it was actually cheaper because the cost of the Western Blot had gotten to be to the point that the differentiation test was actually cheaper. They indicated that it was actually saving them money by using the algorithm.

Mayo Clinic tended to say that it was pretty comparable, maybe slightly more expensive for the new algorithm.

However, for the most part, no one has said it is significantly more expensive, which is good. We can diagnose acute infection. We can better diagnose HIV-2.

Sop, why is this important? Obviously, there is a huge public health benefit to early diagnosis. There have been many, many studies looking both at behavioral aspects, the actual infectivity of people, et cetera.

For example, a very – now quite an old study talking about the transmission rate was higher in unaware groups compared with people that knew their status. People – once again, more behavioral related, people with acute infection named more partners. They had more partners also with undiagnosed HIV compared with people that had longstanding infection and knew about it.

There has been modeling data in the MSM population suggesting that the epidemic would be much larger without behavior change. There is higher rates of transmission. Some of the early work was done in Rakai in Uganda.

Depending on the study, it is anywhere – suggested anywhere 10 to 26 times the infection rate can be higher in people that are in acute infection.

There is actually one primate study that suggests it is not just the viral load, but the actual viral particle, itself, is more infectious in the early stage. It was never quite determined why. They have actually done some studies in humans. I saw several studies presented by Beatrice Hahn. It appears to be the case in individuals. The exact mechanism isn't known. It may simply be that having some antibody bound to the virus once there are antibodies being made decreases the infectiousness of the particle even though it is not neutralizing.

Then the next benefit basically is that treatment as prevention works. There have been multiple studies now. Obviously, the first one was by Mike Cohen, the HPTN 025 trial.

There have been many subsequent studies, including the Partners trial that came right after that. This was also true for MSM. The HPTN was primarily – was

heterosexuals. The Partners study was both heterosexuals and MSM. Basically, there was a huge reduction. In HPTN, it was like 96 percent reduction. Partners it was essentially 100 percent. So it is important to diagnose people early.

Now, we actually have evidence that there is individual benefits for early diagnosis as well. There is early data that indicates there is preservation of immune response and immune function, a decreased viral load, viral reservoirs. There has now been randomized control trials that indicate that the risk of death or severe illness is lower when ART is started early. The first one was the START study.

We also – very recently there has been some data to indicate that if people are diagnosed in the acute phase, they are more likely to be linked to care, initiation of viral therapy happens sooner, and viral suppression is also quicker than people with established infection.

I have to put this up. I think this is one of the impetuses - a paper that came out from Dr. Branson in which Joanne Stekler was the editor – to basically indicate that we are updating technology. We are updating algorithms. So it is important to also think about updating the regulation of HIV tests. I think that is why

we are here today. I greatly applaud FDA for making this decision to have this advisory committee meeting.

I want to talk about a couple of other reasons. I said I would mention it before. It is not just the early phase of HIV infection and decreasing – improving that last 15 percent of people that don't know their status. We are also worried about the people that we can prevent from getting infected by testing.

That is related to PrEP and pre-exposure prophylaxis. There is considerable evidence now that daily PrEP can reduce the risk of getting HIV. Studies have shown that it can be greater than 90 percent for MSM. Even people who inject drugs, it can be greater than 70 percent. PrEP definitely has the ability to change and prevent people from getting infected.

However, testing for PrEP is extremely important and continuous basically. It is important to be able to detect acute infections both to prevent putting someone on PrEP that is acute infected and potentially creating drug resistance. But also for people that are taking PrEP, we want to be able to determine if they get infected very quickly. We need to be able to test easily and readily for acute infection.

The other thing is if you are on PrEP, it is required that you have to be tested every three months,

once again to make sure you haven't become infected with HIV. You must do this to get your refills for PrEP.

Obviously, we want testing technology that can optimally detect infection as soon as possible either with nonadherence or not optimal adherence, which has been shown to be a problem with PrEP. People do need to take their meds as prescribed. We know that some people struggle with that. Also, in cases where there is PrEP failure and potentially that person gets infected with a strain of virus that is already drug resistant.

There is a huge estimated need for PrEP. CDC has estimated that one in four sexually active MSM that are not infected could benefit from PrEP, one in five who inject drugs, and one in two hundred even in HIV-negative heterosexuals with ongoing sexual activity and high risk. So, it is estimated that overall about 1.2 million people could benefit from PrEP. Obviously, that is a lot of testing and a lot of testing that needs to be done to determine if there is acute infection or PrEP breakthrough.

I want to talk a little bit about point of care. This is actually a van from Baltimore. I actually went out. It is a really interesting experience. I am a laboratorian by training. I don't normally interact with people. I actually – as far as – not interact with people, but you understand what I am saying, as far as patients or

on the ground. I actually was able to do this. It actually changed my whole perspective about testing and the importance of being able to get to people where they are.

This was actually a shot from the National HIV Behavioral Surveillance system we have at CDC. This was like at two o'clock in the morning. We were actually out on the street corner trying to get people to get tested, high-risk, and to do a behavioral survey.

Obviously, point of care testing and home testing can be important. Some people do not want to be engaged in the normal health care system, but they are willing to go to facilities to be tested in rapid situations.

Point of care tests are important. We want to be able to - everyone to get tested. One caveat about that. We know that oral fluid assays may miss acute infections. It is very important that people understand that are being tested, the limitations of the test that they are being tested with.

There is a fair amount of evidence that using test in the point of care in these testing vans or in STD clinics, et cetera, can help with improved linkage to care, which is important based on the cascade I showed you. We would very much like to have additional rapid antigen/antibody test or point of care nucleic acid test so

that we can get these people in these vans potentially to know that they are acutely infected.

Previously, when the oral fluid test was coming before FDA for consideration for over the counter testing, FDA actually did a model suggesting that there could be a huge benefit for rapid over-the-counter testing.

I just want to say a couple more things. CDC has been involved actually since the beginning in evaluating tests and how they perform. I showed you some data from the testing we did to look at seroconversion and when tests become reactive compared to when people are infected.

But CDC has been doing this not just in the laboratory. They have evaluated rapid tests in the field. They have done post-marketing surveillance of rapid tests when they first came on the market.

There is currently a project going on right now, something called DETECT. It is actually a prospective evaluation in a clinical setting looking at unprocessed specimens. They are currently evaluating head to head oral fluid – both of the oral fluid tests that are on the market. They have been evaluating the antigen/antibody combo test and the INSTI test.

They have also been able to take those same samples and look at fingerstick for the HIV-1/-2

differentiation assay that is out there now. They are also collecting specimens.

They hope to add rapid NATs, actually some before they are through FDA, but as a pilot research study. That is hoped to happen this fall.

Once again, CDC – I want to make this point. CDC very much wants to get people diagnosed, but we also want to make sure that it is working well. CDC continues to plan to do both pre and post-market evaluation of tests to determine performance not just in the lab, but also in the field.

What are some anticipated advantages we think at CDC for test reclassification? Hopefully, there will be decreased cost to manufacturers. Incentive to bring new technology to the market, NAT for diagnostic purposes, for example. We really think that is important because of PrEP and also just getting people on therapy quickly since treatment is prevention works.

We hope to have additional HIV-1 differentiation tests. We kind of feel that it is never good just to have one option. It is always good to have more than one.

We hope also maybe if down-classification happens, companies might be more inclined to look at different specimen types such as DBS, which can be important in surveillance situations.

Hopefully this will decrease the process time for getting tests to the market. It will also hopefully lead to improvement of algorithms, which is basically what I put up here. This is the current one. If we had easy to use or more nucleic acid tests, we could use them as the second step in the algorithm, particularly for those people that are p24 reactive. It would greatly decrease the overall turnaround time for diagnosing people with acute infection.

The current NAT that we have on the market isn't used in very many places, at least the one that is FDA-approved with a diagnostic claim. Most people don't want to use NAT as the second step because it is not cost-effective or really feasible.

Just a summary. I am really getting close to the end. What would be the impact of new technology if it did come to the market? Like I said, we could simplify algorithms, both in the laboratory. Hopefully decrease turnaround time. More rapidly diagnose acute infection.

In PrEP clinics, it is important both for initiation of PrEP and monitoring with that. We hope we can get the first dose of PrEP to people sooner.

Now, there is a series of – since the testing has to happen, it can take a while to happen – there has actually been a demonstration project in San Francisco where they have tried to get PrEP to the person the day it

happens. It is a series of tests. Once again, they are actually using the viral load test that they verified off-label to get people on PrEP hopefully on the first day that they come.

In the context of HIV care, hopefully improved and additional tests will help both initiation obviously for testing, reengagement in care – often times, people that get out of care end up going back through the whole testing algorithm even though they have had documented infection before.

Then obviously, monitoring. If we can get to the point that we have viral load tests that also change classification in the future then we can streamline the monitoring as well.

Obviously, there are some challenges and solutions that FDA has to deal with. I certainly appreciate that.

There is the potential for decreased test performance and quality. As indicated in your briefing packet, there are safeguards that will be in place because of the special controls. I know FDA is going to talk about those ad nauseum. I am not going to talk about that. I just wanted to say that we think that FDA using special controls that we can mitigate some of this risk.

The other thing I want to end with is we, at CDC, really feel that reclassification of HIV test is just another step in normalizing HIV testing. There is still some stigma associated with HIV. Everything we can do to make HIV a more normal disease, whether it is down-classifying tests or a whole host of other things, we feel it can help with that stigma.

Many of these slides have been presented previously by a whole host of people – I just want to say that – including Dr. Branson, who I know is in the audience.

That is it.

DR. CALIENDO: Thank you, Dr. Owen. We are going to hear from our next speaker and then we will have time for questions.

Our next speaker is Dr. Hardy from Whitman-Walker Health. He is going to be talking about clinical application of HIV testing technology: how are they really used in the community.

Agenda Item: Clinical Application of HIV Testing Technology: How They Are Used in the At-Risk Communities

DR. HARDY: Good morning everyone. What I am going to be speaking about is sort of the other side of the coin. You just heard a very, very wonderful, detailed, and clear demonstration of how HIV testing has evolved over the past

30 plus years. Now, what I was asked to do by my FDA colleagues was to talk more about how it actually is carried out in the everyday world.

I spent the first part of my career, starting in 1982, as a caretaker for HIV positive persons. I have continued on through that to the present time. I started off in Los Angeles, where the epidemic was first recognized. I stayed there until just recently when I moved to Washington, D.C.

During that time, I worked both as a full-time academic clinical researcher and also basic science researcher. I decided to get back into my – getting into more of the nitty gritty of how HIV is treated, so I came to Washington, D.C., because D.C., as you know, has one of the highest prevalences of HIV infection of any place in this United States.

So let me kind of give you a little background about what I am going to tell you today. Whitman-Walker Health is where I work. Whitman-Walker is a historic LGBT care center. It has been in existence since 1973. It has been incorporated since 1978. We are celebrating our 40th anniversary this year.

We are now a federally qualified community health center, which means we take care of anyone who walks in the door. We actually have a very strong mission to be able to

care for the diverse urban community throughout Washington, D.C., with emphasis on LGBT and HIV health.

We have two different healthcare centers in the District of Columbia, one in the northwest area, a very new, nice looking center on 14th Street, and also a center, a little bit older, called the Max Robinson Center in Southeast on Martin Luther King Boulevard.

We really are a primary care medical area facility. We also work in women's health. We have infectious disease specialty care, pharmacy, research, which I am in charge of currently, dental, behavioral health of all kinds, medical adherence case management, legal services, youth services, and community health. I show this to you because we really try to be what is really called a medical home, a one-stop shopping area for patients to come and after diagnosed or before diagnosis avoid or treat their HIV infection.

Our demographics are shown in the next few slides. In 2017, we served a little over 15,000 unique patients. We completed over 115,000 encounters. We have about 10,000 medical patients and about 4,500 of these patients are HIV-positive. Currently, we care for about a third to 40 percent of all HIV-positive persons in the District of Columbia and the areas around the District.

Here are the demographics of our clinic. As you can see, the District has been broken up here into the usual wards. The great majority are – patients come from Ward 1 and 2, the 18 percent and the 13 percent there, which is the area that is most central around Northwest, around the Dupont Circle area. Our other high impacted area are the Ward 7 and 8 in Southeast D.C.

As you can see, 70 percent of our patients come from the District of Columbia, but we also have about 30 percent that come from other parts of the DMV, as we call it.

In terms of race and ethnicity, 40 percent of our patients are Caucasian. Almost 40 percent are also African-American. About 12 percent are other, not choosing an ethnicity. About 15 percent are Hispanic.

We have about a 50-50 split of persons who are coming for HIV care versus other care.

70 percent of our patients are men. 25 percent are female – identify as female, I should say, gender-wise. 6 percent actually identify as transgender. We have one of the highest transgender populations of any clinic in the U.S. as well.

As far as orientation, this is a thing I always find very interesting. Less than half of our patients

identify as being homosexual, bisexual, or lesbian. The majority identify as being heterosexual.

In terms of age, it is really kind of split. Most commonly are individuals who are less than 30, in the 40 area. Smaller numbers as age increases. It is a pretty young-based clinic as well.

In terms of our – one of the first things we started doing when HIV testing became available was to set up ways for people to get testing easy and to make it more accessible. Of course, this is really what increases the ability for persons to, of course, find out about their infection, alter behavior, become treated. If they are negative, at this time they can also start on PrEP or preexposure prophylaxis. HIV testing has been a very important part of what we have always done.

We offer confidential HIV and STI testing to the general public at all three of our locations and also through a mobile unit. The other location that we offer it at is a non-clinical care place specifically for youth, anywhere between the age of 12 up to 30. All services for HIV testing and STI testing are both confidential and free of charge.

Those are the places where we do it.

We also have a program called Testing Together in which we have a specific service for individuals who are in

a relationship, MSM or heterosexual, and want to be tested at the same time to really be able to understand their risk for safe sex between the two people.

Our mobile van is a very important part of this. As Dr. Owen already indicated, this is really the way that a lot of the testing that we do now actually happens in the District of Columbia.

Our van moves around to many different locations throughout the District of Columbia, including the two most well-known sex clubs. We test there at least once or twice a month. A large transgender homeless shelter as well. We really try to make sure that we bring the testing to wherever people are, including different kinds of events, bars, et cetera.

We really try to focus on the at-risk communities, which are basically 18 to 24 year old MSM, particularly MSM of color, and also 24-35 year old heterosexual African-American women. About 30 to 35 percent of our HIV-positive patients are, in fact, female, which is very different than many places around the country.

We also, of course, want to look at heterosexual African-American men under the age of 40, who have a greater than other incidence of HIV infection. Of course, we also make sure that we work with sex works and homeless

populations and also youth down to the age of 13. In the District of Columbia, we can test individuals for HIV without their parent's permission down to the age of 13.

We actually do a STI self-test kit. We ask the individual to swab themselves, their throat, their rectum, and give us a urine specimen. We have found that self-swabbing actually works very well compared to care provider swabbing. Again that is part of the whole kit that we do when someone comes in for testing.

We do a lot of what is called post-exposure prophylaxis. I think this is a very important thing that really depends entirely upon HIV accurate and rapid HIV testing. We treat probably somewhere between two to seven new individuals per week with post-exposure prophylaxis, individuals who feel like they have had primarily sexual exposure to HIV. They know at the last test they were negative.

Basically, what we do is bring them in and start them as quickly as possible, but always within 72-hours on a full antiretroviral regimen in order to try to prevent the acquisition of HIV infection.

This is something we have been doing since this sort of treatment has become available. We actually do this much more than many ERs in the District of Columbia

because we are set up to do it pretty much around the clock.

We think that it is around 80 to 90 percent effective at preventing HIV infection, although one must admit there has never been a clinical trial and probably never will be to really prove this.

It really depends upon whether or not a person has a positive test or not. If they are negative at the outset, then putting them on medication probably doesn't hurt them for the 30 days they receive it. If they are positive and they don't know it yet, then they will simply be treated with a full regimen. If they are in the midst of the beginning of seroconversion, what effect early treatment actually at that point would have is still yet to be clearly understood.

Pre-exposure prophylaxis is something we do even more so in our clinics. Soon after the FDA approved pre-exposure prophylaxis in 2012, we started doing different research studies with PrEP in the United States, both a demonstration project among MSM and then later a study that was funded by the CDC in which we showed we could incorporate PrEP into primary care.

I think this really is a place where testing could be very, very much improved. There is always a waiting period between the time that a person comes in

indicating they are interested in taking PrEP and when we can actually safely give them a prescription or give them the tablets to start the medication to prevent HIV infection.

The most dangerous thing about PrEP and really probably the only really dangerous thing about PrEP in most patients is treating someone who is in the midst of seroconversion. Several cases have demonstrated while doing this you can create HIV resistance by giving them an incomplete HIV treatment regimen of only two medications as opposed to the required three.

Reliance upon a rapid test is really important here. What we have found is about 10 to 15 percent of our individuals who come in and ask for PrEP and are waiting for the test results to come back – we do an initial Rapid test to make sure they are negative. As you have seen, the Rapid tests are not that great for really feeling confident about acute infection. We actually do a p24 antigen containing test – antigen/antibody combo before we actually have the person start the medication just to be sure we are not using PrEP in a dangerous way.

That is when we actually lose most of our patients. They tend to stop. They tend not to come back. They tend to not pick up their prescription in that waiting period. There is a very important period of time when a

person has made a decision to start PrEP that we need to get the medication started.

We have not started using viral load testing as was mentioned is being done as a pilot program I guess in San Francisco. For one thing, the cost of that is very high. The turnaround time is still about five days. So a rapid test that would be like a NAT test could be very helpful here.

Just to look at the positive Rapid tests that we have been doing, we actually use the INSTI test that Michelle showed on the graph earlier. As you can see, the number of new HIV-positive tests that we have been doing over the past four years, between 2014 to 2017, has actually decreased while the number of total tests has actually increased up to a high of almost 12,000 tests in 2017.

The other thing that has really been interesting in the District of Columbia is that in 2006, it was noted by the D.C. Department of Public Health that the prevalence of HIV in the District was around three percent, higher than any other metropolitan area in the United States. That varied from as high as seven percent in the Southeast quadrants up to as low as one percent in the Northwest quadrant. There is a very significant gradient.

As you can see in the bottom panel there, the positivity by zip code has actually decreased, getting lighter and lighter, turning from orange or red to pink to gray, indicating that testing, intervention, treatment, and PrEP is probably having an impact.

So, as you have already seen, this is the algorithm that we use. It is a little bit different than what Michelle told you. We start off by using a point of care Rapid Test, an INSTI test, which is only a third generation antibody Rapid test, or an OraQuick, an HIV-1 and -2 point of care Rapid test, as a way to try to initially look for HIV antibodies.

If that is non-reactive and the person is negative for HIV-1 or -2 antibodies, then we actually do counseling and offer those persons PrEP.

If it is reactive, then we actually start a chain of events called the Red Carpet program. Patients are immediately or at the most within 24 hours, introduced to a Nurse Case Manager, who takes that patient and actually sets up the confirmatory HIV-1/-2 antigen/antibody fourth generation test. Then also does viral load, CD4 cells, and genotype of the virus. While this is happening, the patient is also introduced to an insurance navigator to get the patient onto either public or private insurance and be able to have the patient ready within 24 to 48 hours to see

a provider and start medication if that can be accomplished, really depending upon insurance.

You saw what Michelle indicated earlier. The test that we use for our screening test is the INSTI test, which has about a nine day better than Western Blot. The test we confirm with is the Bio-Rad Antigen/Antibody Combo test, which has something around a 19 day better than Western Blot test. It is still not as good as what a Gen-Probe test could actually do.

So, let me give you a couple of clinical scenarios, which are real, and kind of put the emphasis on how these tests can really make a difference or could make a difference if they were, in fact, better.

JRR is a 24 year-old transgender woman. Recently immigrated to D.C. from El Salvador. She is currently seeking asylum in D.C. due to persecution and abuse due to her gender identity in El Salvador. To support herself, she works as a domestic worker for cash under-the-table and also at times as a sex worker.

She comes to Whitman-Walker for gender-affirming medical and behavioral health services. She is offered HIV testing, but refuses due to fear of deportation, stigma, and loss of work.

She was convinced by her housemates, however, and she agrees to take an HIV rapid test, an INSTI. The test reads out as being positive.

Overcome by fear, anxiety, and lack of health literacy regarding HIV treatments, she attempts suicide by overdosing with acetaminophen and benzodiazepines. Her housemates discover her and take her to the hospital where she is diagnosed with severe liver toxicity.

She does ultimately survive and returns to care at Whitman-Walker.

One of the problems here with this kind of scenario is that when we tell a person that their initial test is positive, we also tell them that it is not confirmed because we have to. It is not a confirmed test. Therefore, very strong and negative emotional reactions can occur in this kind of situation if we cannot get a patient into care rapidly and make sure that the support is needed there by telling them that they are truly HIV-positive. That is something that there is a lack of in situations like this.

What this basically is saying is that we caught the patient there at the Rapid test. We never got a chance to do the confirmatory test and an adverse sort of event occurred in the meantime of potential suicide by overdose.

In terms of public health early diagnosis benefits, also doing research – as Michelle has already showed you, the ability to try to decrease transmission between acutely infected individuals and others is pretty clear not only in animal models, but also in modeling from looking at the infectivity of viruses derived from individuals who are acutely infected.

I think that is one thing that we are really moving closer and closer to all of the time. It used to be a controversy of when to treat HIV infection. We now, since 2012, made it highly recommended that all persons who are positive, regardless of your immune status or viral load, become treated as soon as possible.

During the time that someone is in acute infection either by clinical symptoms and signs or by a positive test like the ones we are talking about today, has really become really the more standard of care. It is thought that by treating persons early that there will be benefits to them down the road.

The other reason, of course, is because of source of new HIV infections often times, but not entirely, is due to individuals who do not know that they are HIV-positive. It is estimated that about 30 percent of all new infections are occurring by those almost 50,000 individuals still in the United States who are not diagnosed.

Also, 60 percent are still caused by individuals who are diagnosed but not into care. Again, that is something where we would probably need to use other techniques, but certainly the ones who are not diagnosed and are transmitting is something we can do something about more rapidly.

In terms of individual benefits for early diagnosis and institution of therapy, as I was mentioning before, the preservation of immune function and also the not quite completely proven, but moving in that direction, idea that we can decrease the viral reservoir by starting treatment as soon as possible.

Many clinical trials within the ACTG and other organizations are looking at this now, getting treatment started as soon as possible. There has been early data that shows the faster someone is treated after infection, the smaller their latent viral reservoir actually is.

Why is that important? If we ever intend to cure someone of HIV infection, having a small viral reservoir, one that is the least heterogenous and most homogenous in terms of lack of evolution, seems to be the easiest way that we are going to be able to cure people of HIV infection in the future.

We are really focusing on identifying people as early as possible, not just when their antibody becomes

positive, but when their antigens or their RNA is positive, and be able to initiate therapy immediately for both individual and public health reasons.

Another clinical scenario is here. MLA is a 30-year-old African American MSM who is sexually active in D.C. He started PrEP about six months ago. He has taken PEP or post-exposure prophylaxis twice in the past year, indicating that he does have some sexual risk factors. He has had rectal gonorrhea twice and syphilis since 2015. He says he does not use condoms, a common statement that I have seen from many, many patients now in the age of PrEP.

He lost his job and health insurance and ran out of PrEP. He comes to clinic with fever, fatigue, sore throat, and rash. His Rapid INSTI test for HIV antibody is negative. His PrEP is continued. A fourth generation test is drawn because the Rapid test was, in fact, negative. Seven days later, the fourth generation test is now positive for the antigen because he is seroconverted, but he is still on PrEP.

This is a situation in which because of this there is a very high chance that his virus will become resistant to one or both of the medications, the antiretrovirals, in the Truvada tablet that is used for PrEP. His infection was not diagnosed fast enough.

Not always are the clinical signs of fever, fatigue, sore throat, and rash recognized as acute retroviral syndrome or the onset of acute HIV infection. In this case, it was not. This individual did, in fact, become resistant to one of the medications in the Truvada regimen.

That is something that could have been I think prevented had we been able to find a way to be able to have a much more rapid test to identify that antigen quickly or a nucleic acid test to do the same thing. We would not have continued his PrEP.

In conclusion and summary, as you have heard before this morning, HIV testing technology has improved incrementally over the past 33 years. The advent of point-of-care rapid testing has greatly improved community acceptance of HIV testing, meaning that no longer do patients have to take the test, wait a week, go through counseling, and then finally get the results.

Getting the results back rapidly is very important. Holding that person’s attention and giving them information about what they are coming in for is very important.

There are still opportunities to improve this technology to offer point-of-care HIV confirmatory tests particularly in order to definitively finalize the HIV

diagnosis and initiate the linkage to care. The point-of-care HIV testing could also confirm diagnosis of acute HIV infection for earlier initiation of antiretroviral therapy.

I will end there and take any question you guys may have. Thank you.

DR. CALIENDO: Thank you very much, Dr. Hardy. That was very helpful.

So, we are going to open up to questions to both Dr. Owen and Dr. Hardy.

DR. ALLEN: Thank you both. Marvelous presentations. Very, very helpful to bring us up to speed.

Question for Dr. Hardy. My experience with HIV antibody testing goes back decades at the CDC, initially. At this point with Rapid testing – we saw photos of the van in Baltimore for testing in the middle of the night. How long does counseling take if somebody is negative by a Rapid test and if they are positive?

Obviously, if we are downgrading and this becomes much more – testing becomes much more available, I am concerned about what the counseling facilities and follow-up is going to be.

DR. HARDY: Well, you bring up a good point because having lived through those days where counseling was so very, very important because the accuracy of the early tests were not very good and part of that counseling

was actually telling people about the test, itself. A lot of the counseling has really now shifted to be able to actually tell the person if you have a positive Rapid test, the chances of you actually being HIV-positive are pretty high. We can't tell you with all certainty that you are positive, but that counseling can occur very quickly and right on the spot.

What we try to do is grab that person whenever, wherever they are and get them into a healthcare clinic as soon as possible. The one thing we have found really important is to collocate or at least co-connecting the testing site and the treatment site. Having those two situations disparate – apart from each other just doesn't work. It relies upon the individual, who is often times very psychologically freaked out, not to actually show up at the clinic. If you grab them and physically help them get there, it can be really helpful.

The counseling does still occur. I think it is more around the fact that we have greater confidence in the accuracy of the test most of the time. We do try to give them some estimate of the fact that we will do a blood test, which will take some time to confirm the diagnosis. We do feel pretty certain with probably 95 percent certainty that they are positive.

On the other side, if they are negative, what has happened in the District of Columbia is that the Department of Health is now requiring us to tell the people who are negative not just the phrase good job, you missed it, go out and have a good time, be safe, but actually grab them also and say PrEP is available. If you are still at risk, here is something you can do about it. Get them into our PrEP services as well.

It still occurs, but it can be abbreviated now because I think the tests are much more accurate and reliable. The level of knowledge in the community has actually increased pretty well as well.

DR. CALIENDO: Dr. Hardy, it is very impressive, the clinic that you have, the program that you have. I am wondering if you could tell us a little bit more about your laboratory capabilities.

The reason I am asking is it looks like you are doing a point of care test. Do you do any – could you do any confirmatory testing? If there was a point of care NAT test, could you incorporate that into your workflow? Just give us a perspective on what you guys are doing laboratory-wise and what you would need to change your paradigm effectively.

DR. HARDY: Great question. Before I came to Whitman-Walker, they actually had their own laboratory

where they did ELISAs and PCR and other sort of automated laboratory tests. Because of cost, like a lot of especially public-funded clinics, we now send all of our laboratory services or needs out to LabCorp. We no longer do much of anything except for point of care tests onsite.

Incorporating a point of care test for a nucleic acid I think would be very simple. It would be very simple. It would actually come into the flow of what we do very, very easily.

We do undergo – all of our testers undergo very rigorous training and certification to make sure that they know how to do the test properly, know how to read the test properly, know how to identify what we think may be an indeterminate because those are the ones that are always the most difficult to know what to do with.

There is, I think, certainly a place for a test like that. It could be incorporated into the clinical flow of what we do very easily.

DR. CALIENDO: I have a question also for Dr. Owen. Can you give me a perspective on the fourth generation tests? How many have separated antigen from antibody? It wasn’t clear to me that the ones that are done in the laboratory actually do that separation.

DR. OWEN: So, there is one laboratory-based test that does that that is FDA-approved. It is called the

BioPlex. There is one Rapid test to determine. There are only two tests.

All of the other antigen/antibody combo tests do not differentiate. You do not know if it is reactivity to antigen or antibody.

DR. CALIENDO: And then the one test that you have to distinguish HIV-1 and HIV-2 is a lab-based test only?

DR. OWEN: It is basically considered moderate complexity, yes.

DR. BAKER: This question is for any of the speakers. I am wondering if you could possibly comment on the impact of changing the classification on schools being a location for HIV testing.

DR. HARDY: I know in the District of Columbia, HIV testing is offered to all high school students in the D.C. Public School System as part of what Dr. Owen mentioned, to try to normalize testing. Trying to incorporate it into what is happening in individuals' everyday life.

HIV testing was also incorporated into the DMV, the Department of Motor Vehicles. In which persons would come in and get their license, their car, and as they were exiting, they said would you like to get tested for HIV, too, do it right here. They did, in fact – they found there was very high acceptance rate for doing that. They

actually started decreasing it because the prevalence decreased so much it wasn't really worth doing it so much, which I think is a good sign in many ways.

I think incorporating it into persons' everyday life like high schools makes great sense.

DR. ESCOBAR: My understanding for the PrEP and the PEP is individuals will go in based on their risk and they will get medication if they were exposed or think they were exposed. It can happen many times a year, I guess, or as often as they want.

Now, doing this, will that at some point have any affect on a Rapid test or will it change any of the testing depending on how often they might take this? Is that an issue?

DR. HARDY: What I hear you saying is probably more related to post-exposure prophylaxis, in which someone feels like they have had a significant exposure risk. Usually, it is a breakage of a condom or not use of a condom with an unknown partner, which happens more than you can imagine.

Repeated episodes of 30-days of antiretroviral medication does not seem to have any effect on antibody tests as long as the person has not seroconverted as best we can tell. Repeated use of antiretroviral medications is not, in an HIV-negative, truly negative, individual does

not seem to really change the way that the antibody test and assay will actually pick up antibodies unless they were really there. I have not seen any situation, for example, where that may be a problem.

There is one – I do need to mention something about PrEP, however. There has been a handful of cases in which individuals who were – most commonly why PrEP fails is because people don't take it. That is the primary reason that PrEP has failed in the past, both in clinical trials and clinical practice.

However, there has been a cumulation of four individuals in the world today who were documented to be adherent with their PrEP, but did seroconvert. Two of them were situations in which the patient was exposed to a highly resistant virus. It was, in fact, genetically resistant to the components of the PrEP tablet.

In one case, that wasn't the case.

In one case, there seemed to be a very strange seroconversion pattern that occurred that kind of threw the usual sort of testing algorithm off. The person had a positive antibody, but had a negative RNA, which didn't really make sense. And then later on, had a positive antigen and RNA in a kind of backward way of seroconversion. Whether that had anything to do with this individual's PrEP is still yet to be really clearly

understood. It has only been one case like that that I have been able to really find.

DR. CALIENDO: Dr. Jones, do you have a question on the phone?

DR. JONES: I have a question for Dr. Hardy. I was struck by when he talked about how much of new HIV infections are diagnosed and not retained into care. I was wondering if you could comment on how much that is due to the time it takes to receive – the lag time in receiving the results of the initial diagnostic test and how much nucleic acid testing or other technologies being rapidly available would change that.

DR. HARDY: I think part of that is once someone is initially told that they are HIV-positive, as you can well imagine, their emotional mindset changes dramatically. The ability to really be able to interact with that person is often times, in my experience and others and it has been well-documented in literature, not very good.

Trying to be as definitive as possible with that individual and not use words like maybe HIV-positive, 90 percent sure, we still have to do a confirmatory test, but you might – we think you're positive only adds to that uncertainty in terms of a lack of a definitive diagnosis to say you are positive, we are going to get you into treatment as soon as possible. It is the inability to

really feel as sure as we can feel in an individual who is in the midst of seroconversion or truly newly positive.

What I have learned is that once those words are uttered from my mouth, the person I am talking to probably hears very little of anything else after that. What I need to make sure of when I tell someone that they are positive is to be as definitive as possible, not sort of well, maybe there is another test we need to do sort of situation and that test is going to take five days.

Let’s get the blood drawn. You go off. We will try to track you down later. I think that is the real problem. If we could have them – if we could confirm the tests at the same meeting that would go a long way of keeping people in care.

DR. OWEN: Just some anecdotal evidence based on that testing in the van that I observed. I actually observed counseling of people that were both told they were not – that the test was negative and positive. I will tell you the way the counselors talked about it is a preliminary positive, but what they focused on is there is that slight chance that the test was not actually correct. Instead of focusing on, okay, I need to get into care, it was more hoping that the test, even though the risk was very small that it was incorrect, that it was incorrect.

DR. CALIENDO: Any other questions? Okay, we are going to break. We will take a 15 minute break.

Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience. We will resume back here at 9:50.

Again, thanks to both of our speakers for excellent presentations.

(Break)

DR. CALIENDO: We are going to resume the session. Our next speaker is Julia Lathrop from the FDA and she is going to be talking to us about the overview of device classification.

Agenda Item: Overview of Device Classification

DR. LATHROP: Good morning. I am Julia Lathrop from the Division of Emerging and Transfusion-Transmitted Diseases in the Office of Blood, and now we are going to move into the FDA regulatory part of the day.

First, I am going to be presenting an overview of how FDA thinks about device classification and risk. Then Anne Eder is going to review FDA's experience with these devices over time and their performance and how actually PMAs are reviewed at the moment. Finally, I am going to present the special controls that we are proposing. They are designed to mitigate any risks that could possibly ensue from their down-classification.

Just as a reminder, the purpose of the panel meeting is to ask the panel to provide input to the FDA on the reclassification of HIV point-of-care and laboratory-based serology NAT diagnostic -- that is, first line diagnostic -- and supplemental devices from Class III to Class II.

In this presentation I am going to give an overview of how FDA considers device risks and classification generally -- this is going to be general principles that apply to how we think about all in vitro diagnostics. I am going to define general and special controls and how they are applied to diagnostic devices and then the reclassification process we are going through today.

First, I want to point out that in vitro diagnostics, or IVDs, are in fact medical devices according to the definition of device in the Food, Drug and Cosmetic Act. The definitions in the Act describe devices as reagents, instruments, systems used in the diagnosis of disease or other conditions in order to cure, mitigate, treat or prevent disease, and intended for use in the collection, preparation and examination of specimens taken from the human body. This is reiterated in the Code of Federal Regulations, and what this means is that IVDs are

subject to the same statutes and regulations that apply to all medical devices.

The basis for FDA review of all IVDs starts with the intended use of the device. The intended use is what the device is intended for -- the condition it's designed for, the population, the sample types that it's designed for. From the intended use then logically flow the risks and the classification of the device.

The intended use determines the risk of the device. For most IVDs, this means the risk to a patient from an incorrect result. There are some IVDs that have collection devices that have some inherent risks, but for the most part and for the vast majority of IVDs we're talking about the risk to a patient of a wrong result.

In this case, it could be a false negative result which could deny a patient needed treatment, or it could be a false positive result, in which case a patient is treated for a condition they don't have, and it could also mean they are denied treatment for a condition that they do have.

In intended use, it is also important to understand that the same device can have different risks depending on the intended use. You could have the identical device -- same reagents, same detection system, same instrument -- but because the intended use is different,

has different indications, it can have both a Class III and a Class II claim. Because the risks associated, for example, with selecting a drug that a patient is going to be taking are not the same as the risks associated with monitoring the status of a patient who has already been diagnosed, the same device can have two different risk classifications because it can have multiple intended uses. But the risk then is mostly -- and what we look at when we think about risk for the most part is -- the risk of a wrong result.

The risk then determines the controls, and these are general and special controls and in subsequent slides I will go into detail what exactly we mean by general and special controls. The risk determines the controls that are required to provide a reasonable assurance of safety and effectiveness. By this we mean reasonable assurance that the device is going to perform as expected.

The risks and the general controls then determine the device classification and, therefore, the type of submission that is required before the device can be legally marketed.

This is just a general overview, and we’re going to go through each of these elements specifically so I don’t expect you to digest any of the particular parts of this table. Fundamentally, this is an overview of the

different device classes and the types of information that are reviewed and required in order for them to be marketed.

Class I devices are devices that have a low or moderate risk, and again, that is a risk to the patient of the impact of a wrong result. Some examples of Class 1 devices are stand-alone instruments. For example, you can have a mass spectrometer that doesn't have an assay associated with it that has been cleared or approved but can be sold for clinical use because labs might want to put their own assay on it. So, as long as it doesn't have an assay but is a stand-alone instrument, that is a Class I exempt device.

Another example is diagnostic controls. Those are generally Class I. These are usually exempt from premarket review prior to being legally marketed. This does not mean that they are not regulated. What it means is that they don't have to provide a submission to the agency before they're allowed to market their device. Exempt devices are not considered cleared or approved and they cannot be marketed saying so. There is a small cadre of Class I devices called Class I Reserved Devices that do require submission of a 510(k), but that's very few.

When devices are exempt, that means they still have to adhere to general controls but the manufacturers have to maintain internal documentation that they do adhere

to those controls, and produce that information when they are inspected. But it's considered that general controls alone -- as I said, we will get into the definition of what those general controls are -- are sufficient to provide a reasonable assurance of safety and effectiveness.

Class II devices are devices that have a moderate or it could be a high risk of impact to a patient of a wrong result. Again, it's important to understand when we talk about risk we are not talking about the risk of the disease to the patient. You can have a very serious disease, obviously, but because special controls can be written, the device to detect that disease can be safely classified as a Class 2 device. Some examples of Class II devices are meningitis, encephalitis NAT tests or tumor-monitoring tests.

Class II devices typically require submission of a 510(k) premarket notification before they can be legally marketed. Those are cleared by the agency based on a definition of substantial equivalence to a predicate device. I am going to define what FDA means when we say substantial equivalence and predicate in the next slide because you hear those terms a lot and it's important to understand what we mean. But they are cleared.

These are devices where general controls alone are not considered sufficient to provide reasonable

assurance of safety and effectiveness and so special controls are written that all devices have to adhere to in addition to general controls to provide that reasonable assurance. So, general controls are insufficient, but there is sufficient information about the device to establish special controls that can mitigate the risks of the device and provide reasonable assurance of safety and effectiveness, and the likelihood of harm or risk from the device can be mitigated.

When we talk about substantial equivalence, substantial equivalence is the standard by which 510(k)s are cleared. That means they are substantially equivalent to a predicate device, a predicate device being any legally marketed device that has the same intended use. It doesn’t have to be word-for-word identical but the same intended use.

Substantial equivalence does not mean that the performance or the technology need to be identical. A mass spectrometer can use an immunoassay as a predicate device if the intended use is the same. Nor does the performance have to be the same. It doesn’t have to be identical. A new device can have a different sensitivity, maybe a better sensitivity than the predicate device, but it has to be substantially equivalent. A manufacturer cannot make a claim that their device is superior, because if they are

saying it’s superior it is not equivalent. If it’s superior, that requires a specific type of statistical analysis for superiority studies.

The take-home is they don’t have to be identical in order to serve as a predicate. A manufacturer can use any legally marketed device with the same intended use as a predicate. It doesn’t have to be their device. It doesn’t have to be a brand new device. Any of those are sufficient to be used as a predicate.

FDA can review any information necessary to make a determination of substantial equivalence. It’s important to understand that the vast majority of IVDs submitted to the FDA are Class II devices. In some cases, they are very straightforward devices. Maybe there’s an international reference standard to demonstrate the accuracy of the performance of the device, and so substantial equivalence could be demonstrated by an analytical method comparison study because it’s appropriate for the intended use and for that device.

However, other devices are very complex and have a lot of nuances that are very specific to that particular device and that particular technology, and can require any information up to and including a prospective clinical study. In almost every case where there is clinical data, the submission of summary line data is reviewed in order to

determine substantial equivalence. The term “substantial equivalence” encompasses a broad range of types of evidence, but this evidence is device-specific and is specific to the intended use of that type of device.

If a sponsor wants to develop a new device and is unsure about what’s going to be needed they can look at the predicates, but we always strongly encourage everyone to come in and talk to us in pre-submission so they understand the path forward and they know what to do before they embark on these studies. So those are Class II devices.

New devices are classified automatically as Class III high-risk devices by default because there is no predicate, so you can’t demonstrate substantial equivalence and there are no special controls, so they are by default considered Class III according to the regulations.

But, of course, not all brand new devices really merit a Class III classification. There is a process called the de novo petition that allows a sponsor to petition the agency to reconsider the automatic Class III designation and consider the device as a Class II or Class I device. This classification is based on a demonstration of the benefit of the device and how that’s compared to the risk of the device.

Petitions are granted and they are based on a demonstration through valid scientific evidence that the

benefit of the device outweighs the risk of the device even though there is no history of the device. It's performance over time. There is no predicate or any way to know exactly what's going to happen, but based on the studies and based on the valid scientific evidence, it supports a determination that the benefits of this device outweigh any risk, and, therefore, it can appropriately be considered a Class II or Class I device.

If a petition is granted, the regulation is written and the device is classified and the special controls are written to mitigate any risks associated with that device.

Class III devices are high-risk devices. A common example of Class III devices are companion diagnostics where you have a drug that's indicated only for patients who have a particular mutation, for example, and there's a test that can detect that mutation and you can't use the drug without testing the patient for the mutation. And if you used it on a patient who didn't have the mutation, they could suffer adverse events without any benefit from the drug. That is a common example of a Class III device.

These devices are of substantial importance in preventing the impairment of human health, and their failure presents a potential unreasonable risk of illness or injury. However, there is insufficient information to

write special controls. It's important to note a Class II device can also be of substantial importance to protecting human health and its failure presents an unreasonable risk of illness or injury, but there is enough information to write special controls.

But with a Class III device there isn't any information so you can't write special controls because you don't know what the risks of the device are necessarily going to be. These typically require premarket approval prior to being marketed, and they are approved based on a review of valid scientific evidence that demonstrates the safety and effectiveness of this device.

Back to the overview of the different classes, just to summarize, Class I devices are low-risk devices. Clearance/approval is not required except for the small subset of Class I Reserve Devices that do require submission. There is no comparator. They have to adhere just to general controls and nothing is submitted, but adherence to the general controls has to be maintained and demonstrated by the manufacturer.

Class II devices are mostly moderate-risk devices and require submission of a 510(k). There are some Class II devices that are considered Class II exempt devices. They also do not have to come in -- just like Class I exempt -- don't have to come in to the agency prior to being legally

marketed, but they are still regulated. And for Class II exempt devices they still have to adhere to any special controls that exist for that device. They don't have to show us that they have adhered to it, but that data has to be maintained in-house and is reviewed when they are inspected.

They are compared with a predicate for substantial equivalence. They have to adhere to general and special controls. There is also the de novo pathway which can be Class II, most common, but you can also have a Class I device when a petition is granted, and they are cleared or granted.

Class III devices are high-risk devices that require approval of a PMA. The performance of the device is compared to clinical truth, and they have to adhere to general controls and the clinical validity of the device, and those devices are approved. When we talk about the device was cleared or the device was approved or the submission, if it was legally marketed, this is what we're talking about. Those terms all have meaning to the specific class of the device and those are also often used kind of generically. You hear that FDA approved things a lot, when they actually mean cleared. Not that it matters particularly except when we say it.

There are similarities and differences between 510(k)s and PMAs in terms of the types of information that is submitted and is reviewed, and how the regulations apply to these. Some aspects of the submissions are the same between the two types of submissions, and we will see this discussed later on about how the special controls that we have written are designed to address any differences between the types of submissions.

As I mentioned a moment ago, Class II devices, the performance standard is substantial equivalence, whereas, the PMA is safety and effectiveness based on clinical validity. 510(k)s may require clinical studies, and again, because the breadth and scope of 510(k)s cover so many different indications, they may require clinical studies. They certainly don’t always; whereas, PMA devices almost always require clinical studies.

The analytical data that’s submitted and reviewed is the same -- sensitivity, specificity, interferences. That information is the same in both types of submission.

Chemistry, manufacturing and controls -- The manufacturer has to maintain internal documentation that they have their design controls in place, that they are adhering to the quality systems regulations, the manufacturing is under control, but they don’t submit that in a 510(k), and the agency doesn’t review that information

prior to clearance. However, for a PMA, this information is reviewed in the PMA before the PMA is approved.

The review of software and instrumentation is the same in both the 510(k) and a PMA. The labeling, in the 510(k) we review draft labeling when the device is cleared. In a PMA we review finally.

There are also some similarities and differences in how the regulations apply to 510(k)s and PMAs. Both have the same schedule of post-market inspection and the same inspection criteria. All medical devices including exempt devices are required to adhere to 21 CFR 803 requirements for adverse event reporting under Medical Device Reports, so all devices have to report adverse events to the public database at the FDA.

Both 510(k)s and PMAs are subject to least burdensome provisions where the agency asks for the information that is necessary to make a determination whether the device should be cleared or approved. There is no premarket inspection for a 510(k), whereas the premarket inspection is customary in a PMA. So there is premarket inspection of the manufacturing facility. There is also premarket inspection, the BIMO, the bioresearch monitoring, which inspects the validity of the clinical trial, the integrity of the data that was conducted for a clinical

trial. There is no BIMO inspection in a 510(k) but it is customary for PMAs.

Changes in critical reagents can require submission of a new 510(k), and there is guidance available, fairly recent guidance that was updated, that helps manufacturers determine when they need to submit a new 510(k) as to what are the critical changes that require the submission of a new 510(k). That information is often submitted in a PMA supplement rather than a brand new PMA.

Importantly, the timeline for review of a 510(k) is half the time for a PMA, 90 days versus 180 days. This is FDA days. This isn't counting any manufacturer hold where they're addressing FDA's comments. The FDA has 90 days for a 510(k) and 180 days for a PMA.

These are differences, and you will see this again later when we discuss the special controls and how we are making special controls to address these differences where they might impact the device performance.

The risks to health from devices are mitigated by regulatory controls, and here I will review what we mean when we say general controls and special controls.

Fundamentally, controls are basic provisions in the medical device amendments to the Food, Drug and Cosmetic Act that provide the FDA with the authority to regulate devices to ensure their safety and effectiveness.

And there's the link if anybody wants to read a guidance about controls.

General controls are the basic provisions in the amendments that provide us with this authority. They apply to all medical devices regardless of class, and they include a number of different basic provisions. Again, these are maintained by the manufacturer, but the evidence that you are adhering to the general controls has to be internally documented.

General controls include such aspects as prohibition against adulteration or misbranding, which basically means you can't make a claim that your device can do what you haven't demonstrated it can do. You can't just say it does something without having evidence to show that it does. If you do, that is adulteration and misbranding and is a violation of the general controls.

General controls require adherence to quality systems regulations -- that's design history controls, design verification -- and good manufacturing practices, or GMPs. Devices are required to adhere to these aspects of the regulations as well.

Manufacturing facilities are required to be listed so we know who's making the devices, even exempt devices. The devices themselves have to be listed so anybody can know which devices are actually being made and

have been listed by the FDA. And, as I said earlier, all devices are subject to the adverse event reporting -- medical device reports to the MAUDE database, and that is a publicly-available database that anybody can look and see what adverse events have been associated with that device.

Special controls are controls that, in addition to general controls, are put in place because they are necessary to provide reasonable assurance of safety and effectiveness. General controls on their own are not sufficient. These are device class-specific regulatory requirements that, when followed, provide reasonable assurances. All devices with the same intended use, even if it’s a Class II exempt device, must follow the special controls that are written for that device class.

They are not written for an individual device. You don’t have special controls that are designed just for the ACME diagnostic HIV test, but they are for HIV diagnostic tests, or HIV supplemental tests or other types of tests, so, the device class. All devices within that class must meet those special controls when you provide a submission and the data demonstrating that the special controls have been met. If it’s exempt, that information is kept internally but is reviewed upon inspection. A failure to follow special controls is a violation of the regulations.

Because special controls are necessary, special controls can be very broad in the sense that any information that's required to provide this reasonable assurance can be included as a special control. Some special controls for devices are very short. It might be one or two points that are specific to that device class that have to be addressed. Some special controls are quite lengthy because there are a number of considerations that are required to provide this reasonable assurance, but they can include whatever aspects are necessary.

Special controls are written in collaboration between the agency and the sponsor, so the agency doesn't just write them and people have to adhere to them when you're talking about a particular device, but they work with the manufacturers to develop the appropriate special controls.

Special controls can include such things as performance standards where it's necessary to specify, for example, a lower limit. They can include such things as post-market surveillance or patient registries if it's important to understand who was actually using this device and what impact it may have. They can require particular types of premarket data. They can require special labeling requirements, whatever is necessary, but don't include every aspect that's possible.

Special controls have to be followed because they are statutory requirements written into the regulation and because they have been deemed necessary to provide a reasonable assurance of safety and effectiveness. We try to be flexible where appropriate. Often you will see phrases like, for example, well-controlled studies must be conducted, but there is no prescription as to what those well-controlled studies have to look like. That's because there may be multiple paths that manufacturers can use to get to that appropriate study. There may not just be one study design that's the right design; there may be multiple paths, but you do have to do a clinical study.

So you will see that kind of flexible terminology, and manufacturers and sponsors are encouraged to come and talk to us if they want to make sure that their study is going to be appropriate and meet the criteria.

However, they can also be specific where it's deemed necessary to provide reasonable assurance that the device is going to perform effectively. For example, there may be something that says, the lower bound to the 95 percent confidence interval must be greater than or equal to 99 percent. And this is important because it has been determined that this type of performance is necessary and needs to be maintained across all devices now and going

forward. So, when they need to be very specific they are written very specifically.

If the special controls are not applicable to your device -- you have the same intended use, but it turns out that technology has evolved since they were written, for example, or there are aspects of your device where the special controls just don’t apply -- it may be that the de novo pathway is a more appropriate pathway to submit the device, in which case then new special controls can be written for that particular device class and it gets a new regulation.

That is the sort of thing that should be discussed with the reviewing division before sponsors develop their device. They come in and ask us what do we think is the appropriate regulatory pathway, and we will work with them to determine the regulatory pathway, and ideally before they get started on all their validation because we don’t want people doing studies that are not going to be necessary. So we encourage manufacturers to come in and talk with us in the pre-submission process at every opportunity whenever they have a question.

The reclassification process we’re undergoing today is for reclassification of HIV devices or serology and NAT, point-of-care and lab-based diagnostic and supplemental tests. The regulatory authority under which we

are pursuing this today is under 513(f)(3) of the FD&C Act. This has been initiated by the FDA. Reclassification under 513(f)(3) can occur if a particular interested party -- and it can be anyone -- petitions the agency to consider reclassification, or the FDA can, on its own initiative, decide that the time has come that it's time to think about reclassifying devices.

This reclassification is initiated by the FDA and is based on our experience with the devices over a very long period of time and new information about the risks and how they can be mitigated. We have accumulated enough experience over time that we can write special controls. So we do believe that the devices are of substantial importance in preventing the impairment of human health and their failure does present a potentially unreasonable risk of illness or injury to a patient. But we also believe that sufficient information exists -- and that is what Anne is going to present -- with these devices to write special controls to mitigate any risks and provide a reasonable assurance of safety and effectiveness.

What we're asking from the panel today is a discussion of the risks and benefits to reclassification. We will present in later presentations our interpretation of what we think these risks and benefits will be, but we

are asking the panel to consider if there may be other risks that we might not have considered.

We are also going to present an overview of the special controls. I will say now and also say later the specific wording of the special controls will be included in the proposed order. Today we are giving an overview of what we're proposing and why we're proposing it. But if there are any additional special controls that the panel thinks we haven't considered and they would like us to consider.

And we're asking for general recommendations. We are not asking to formulate the special controls today, but just general recommendations if they feel that this is appropriate. And that's reflected in the question that is going to be asked of the panel.

What's going to happen next is we will write a proposed order that will be published in the Federal Register seeking public comment. At that time, the precise wording of the special controls will be included. Anyone in the public will then have an opportunity to comment on the specifics of the special controls -- if they think they're good, if they think they are not clear, any of that sort of information. It's published in the Federal Register and the docket is open for about 60 days and available for comment.

FDA considers and responds to all comments to the proposed order, so we will take them under consideration. Based on the comments to the proposed order and based on the comments and feedback that we get today, we will issue a final order identifying the appropriate class with a device-specific regulation after the proposed order clears and we have time to digest everything and make a final determination.

If the determination is that, in fact, these devices should remain as Class III PMAs, they will continue and everything will go on as it has been. If the determination is made that we can appropriately classify these devices as Class II devices, new devices will be submitted as 510(k)s. They can use the existing devices as predicate devices, and the existing devices will be reclassified into 510(k)s. What that means for those manufacturers is they are released from the requirements for PMAs in your annual reports. A lot of the requirements to maintain a PMA will no longer apply to those devices, and they will get a letter telling them that this is the case. But all devices will have to follow the special controls.

So that is what’s going to happen after this meeting, and we are very much looking forward to the

discussion and input from the panel on this proposal today. Thank you.

DR. CALIENDO: Thank you. That was very helpful. Our next speaker is Anne Eder and she is going to talk to us about the current status of HIV diagnostic devices.

Agenda Item: Current Status of HIV Diagnostic Devices

DR. EDER: I am Anne Eder. I', a deputy director in the Division of Emerging and Transfusion-Transmitted Diseases in the Office of Blood, and I am going to talk about the current status of HIV diagnostic devices.

This is the proposal, to put it in front of you again. The proposal is to reclassify HIV serology and nucleic acid test point-of-care and laboratory-based diagnostic and supplemental tests from Class III to Class II.

The objectives of my overview are to describe the reclassification proposal and the background supporting the proposal, describe how FDA currently reviews HIV diagnostic device submissions, and describe the historic test performance and adverse events reported for HIV diagnostic tests.

Dr. Owen showed a similar timeline of the advances in HIV diagnostic tests. This one shows FDA approvals over the course of 30 years and the major

milestones dating from the first HIV test in 1985, which used a viral lysate to identify HIV-1 IgG. The tests improved with each subsequent generation with the use of recombinant or synthetic antigens, detection of HIV subgroups, detection of IgM as well as IgG, the first claim for p24 which led to earlier diagnosis and shorter time between infection and detection, and the first claims for other sample types.

The point of this slide of course is to show you, to illustrate that FDA has over 30 years of experience, and as the field evolved and the test technology advanced, FDA acquired the experience to regulate these devices to ensure safety and effectiveness.

Now I am going to discuss the details of the proposal and the devices in the class of HIV diagnostic tests.

HIV diagnostic tests are currently regulated as Class III devices. They require approval of a PMA prior to marketing. They are classified by product code MZF, and this is not an abbreviation for anything but the code assigned to HIV diagnostic devices so that you can search for every device in this class in the various FDA databases.

The universe of tests that we’re talking about today, the current universe of marketed devices in this

device class are the first-line or initial diagnostic tests, and these are the eight point-of-care diagnostic serology devices and 12 lab-based diagnostic devices, all of which are serology and one of which is a nucleic acid test. The proposal also includes the supplemental tests which are six supplemental serology devices, which are a subset in this device class. So we are not discussing any individual test in this class; we are considering them as a class of devices that are currently regulated as Class III in this proposal to down-classify to Class II.

The tests included in this proposal are HIV point-of-care and laboratory-based serology and nucleic acid tests, diagnostic and supplemental devices that are identified by the following general intended uses and exclusions. These are shorthand examples on this slide. The wording might vary among the devices but they all specify that the test is intended to be used as an aid in diagnosis.

The point-of-care test identifies it as a point-of-care test to aid in the diagnosis of infection with HIV. If it doesn’t say point-of-care, it’s a laboratory-based test to aid in the diagnosis. The supplemental tests are a subset of the diagnostic tests in this class and they serve as an aid to diagnosis as an additional, more specific test for HIV.

Notice that a common element in all of these intended use statements is that it excludes blood donor screening. To drive this point home, blood donor screening tests are excluded from this proposal. These devices are approved as BLAs, biologic license applications, regulated under the Public Health Service Act and, therefore, are not subject to classification. Blood donor screening tests are off the table and they are identified by this intended use statement.

The next few slides show other tests that are excluded from the proposal because they raise different issues of safety and effectiveness. Home use, over-the-counter tests require different special controls to address issues specific to the devices including the use as an over-the-counter test. These devices have the following intended use where they are identified as over-the-counter tests, as an aid in the diagnosis of HIV. We are not asking you to consider these devices in today’s discussion.

Viral load tests are currently Class III and they are excluded from this proposal. The intended use of these devices is for monitoring patient status which means that they are intended for a different patient population that is already diagnosed than for aid in diagnosis for those not yet diagnosed. So they raise different issues of safety

and effectiveness that would require different special controls.

The tests must be validated in different populations specifically to address issues related to such use in known HIV-infected patients -- for example, to correlate viral load with clinically meaningful changes in patient management. These are not included in the exercise today to reclassify the diagnostic devices that are used as an aid in diagnosis. They could be considered in the future but it’s just not in the discussion today.

Finally, tests for phenotypic drug resistance are not included in this proposal. These tests are under development and performance standards and study designs necessary for approval have not yet been demonstrated.

These are the eight point-of-care tests that are currently available. I don’t expect you to read the details on this slide but they’re here if you want them and that is the point. We’re not discussing any particular device on its own; we are considering the entire class as a whole and these are the devices that would be affected by the reclassification.

These are the 12 laboratory-based diagnostic devices that are currently available and these are the devices that would be affected if the devices are reclassified.

And these are the six supplemental devices that are currently available.

In the next part of the talk I am going to describe how FDA currently reviews HIV diagnostic test submissions, describe the elements of review, the basis for approval, and the performance in the adverse events reported for the first-line HIV diagnostic tests. The same principles apply to the supplemental tests because they are used as an aid in diagnosis, but the comparisons in this section are with the first-line tests.

This slide summarizes what FDA looks at in a PMA submission -- some of the elements, not all of the elements -- to focus on the key aspects of review and how they are specific to HIV diagnostic devices. Some review elements of study design and analysis are not particularly HIV-specific so I am not going to talk about them. CMC and software, for example, each have their own considerations but they are not class-specific. Likewise precision and reliability standards usually follow CLSI standards.

But I am going to point out some HIV-specific key elements, specific considerations in review of the HIV diagnostic devices in terms of clinical performance, which requires specific sample types and studies to demonstrate clinical sensitivity and specificity, analytical performance and labeling.

This slide highlights clinical performance of the first-line HIV diagnostic tests as an example of HIV-specific elements of PMA review. The basis for approval of the clinical performance is shown in the aggregated summary on the slide. The performance for clinical sensitivity of these devices must be evaluated for all analytes claimed -- HIV-1, HIV-2 -- all sample types claimed. Similarly, clinical specificity must be evaluated for all populations claimed -- low risk and special populations -- in all analytes claimed.

The table shows for point-of-care and the laboratory-based diagnostic tests the point estimates for sensitivity and specificity, the sample number and the lower bound of the 95 percent confidence interval, showing the basis for approval of these tests and the very tight range for sensitivity and specificity and the number of subjects included.

For the point-of-care testing, the lower bound of the 95 percent confidence level is above 98. For laboratory-based, the lower bound of the 95 percent confidence interval is above 99. So these data must be demonstrated with every sample type that is claimed, and this has been the basis for approval of all of the devices available.

These data are shown graphically on this slide. What's important about this slide is the impression it leaves you with or the big picture, but I am going to spend some time to describe the details. The clinical performance data of the tests of the approved point-of-care diagnostic devices in this class is shown for the eight point-of-care tests for every sample claimed. These tests are arranged chronologically in the order in which they were approved.

Sensitivity is shown in orange and specificity in blue with the point estimates for sensitivity and specificity in the 95 percent confidence range. The size of the bubble is proportional to the number of subjects in the study with the reference circle shown here.

The big picture that the slide leaves you with is all of the tests meet the performance of having a lower bound to the 95 percent confidence interval above 98, and this has been constant or maintained over time. The performance that has been the basis for approval has been maintained with the lower limit of the 95 percent confidence interval above 98 percent.

Similarly, for the approved laboratory-based diagnostic tests, the performance is consistent over time. And, again, the same data are shown for the laboratory-based tests on this slide and you can see that for all of them in the order in which they were approved. In this

case, for laboratory-based, the lower limit of the 95th percent confidence interval is above 99 percent.

The big picture is that all of the devices meet the performance that we are proposing in the special controls. And since this has been maintained over time, we have a good understanding, a good database of experience to understand how they should perform into the future.

Another HIV-specific element of PMA review in analytical performance is shown on this slide. For analytical sensitivity these are the types, the numbers and the types of samples that have been the basis for approval for analytical sensitivity, and for analytical specificity these are the numbers and types of samples that have been the basis for approval of all current devices.

FDA also reviews the final labeling which contains some HIV-specific limitations. Warnings and precautions tend to be generic, but limitations that are specific to the device are included in labeling. These are important for correct use or interpretation of the test, and as new information becomes available the labeling should be updated.

Separate from the review of the submission, FDA also monitors adverse events for the device class that are reported under the MZF product code. I mentioned the MZF product code, and this is the power of being in a class in

that you can search all FDA databases to identify this information.

The information is summarized on this slide for the HIV diagnostic devices. More than 100 million tests have been distributed since 2000, but fewer than 1,000 adverse events have been reported through medical device reporting and other sources through July 1, 2018. There have been no recalls under this product code.

While a review of adverse events may raise a particular concern about a specific device, FDA has the authority to investigate and take action, and this authority would not be changed with the reclassification. The take-away is, based on this information, the performance over time of the HIV diagnostic device class raises no safety concerns.

In summary, FDA has been reviewing HIV diagnostic devices for 30 years. More than 20 devices in this class have been approved. The performance is consistent and consistently high among devices in this class, and there are no concerns about the safety as a class of devices. So we conclude, based on FDA’s experience with this class of devices, that the devices are of substantial importance in preventing impairment of human health, and their failure presents a potential unreasonable risk of illness or injury, and sufficient information exists to write special

controls to mitigate these risks and provide a reasonable assurance of safety and effectiveness.

Where there are differences in the elements of FDA review between a PMA and a 510(k) are the ones that will be covered in the special controls, and these will be discussed now by Julia.

DR. CALIENDO: Thank you very much. That brings us back to Julia Lathrop to take us through the special controls that are being proposed.

Agenda Item: Overview of Proposed Special Controls

DR. LATHROP: Anne has just described our history and experience with these devices and the elements that are currently reviewed in a PMA. Earlier I presented the differences between a PMA and a 510(k) submission and what is and is not included in those different submissions. These differences if not mitigated could lead to risk to health if they led to a degradation of the performance of these devices, which have a very strong track record of being excellent devices that are very safe and very effective. So here I'm going to present the special controls that FDA is proposing to mitigate the risks that might ensue from reclassification.

The benefits that we anticipate from reclassification from Class III to Class II include that we

think it could facilitate the submission of innovative devices, and we have heard that there remain opportunities for innovation in this field and we would like to see those coming in and getting into the clinic. Given the review time cut in half, this could decrease the time to market and expedite patient access to these new devices.

In keeping with the least burden principles of FDA review, we think we can maintain the safety of these devices while decreasing the regulatory burden on sponsors. But there are risks that could result from reclassification of these devices. Because there is no pre-approval inspection it’spossible that a manufacturer might be able to manufacture enough of their device reliably in order to get through clinical studies but, over the long haul, they might not be able to continue to manufacture the device, and those deficiencies might have been discovered in a pre-approval inspection which isn’t going to happen with a 510(k).

In addition, there may be s change within a device that affects the performance that the manufacturers might not report. For example, something they might think would be annual reportable in a PMA would not come in in a 510(k).

The reason that these risks to reclassification matter, of course, is that they could increase the harm to

patients from a wrong result. A false negative arising from a device malfunction could, of course, cause a patient to be denied or delay needed treatment, and a person who is given a negative test result may unwittingly transmit the virus because they have been told that they are negative. So that is a very significant risk to public health. And, of course, as we have seen, the loss of care of these patients is a very significant risk.

A false positive from a device malfunction can lead to initiation of unneeded treatment. If they have got a different condition instead of HIV infection, they are not going to get treated for the condition that they have, or they may not need anything at all. It could cause an unnecessary C-section in a woman who is in labor and is first tested when she is in labor and, given a positive diagnosis, it can lead to an unnecessary C-section and treatment of the woman and infant with anti-retrovirals which are not needed because it was a false positive. And, of course, it can cause significant patient distress. This is a very serious consideration that we have about if bad devices were to result from the reclassification proposal due to the differences in a PMA and a 510(k).

As we discussed earlier, special controls are put in place to mitigate these risks. You have seen this slide before, which is what’s reviewed in a PMA. Here is a

general overview, and I will go into great detail on exactly what the special controls are that we are proposing, but here just how we have designed the special controls to mitigate the risks about the differences between PMAs and 510(k).

For example, we have the performance criteria. In all the PMAs, as Anne showed you, the lower bound of the point-of-care devices is greater or equal to 98 percent; the lab-based are all greater than equal to 99 percent. We are proposing a special control to maintain this performance standard, and I will get into the details of that in a few moments.

PMAs have always required clinical studies. We are going to propose special controls that require the submission of clinical studies. There is no pre-approval inspection. Well, there is in a PMA; there is none in a 510(k), so we're proposing that manufacturers submit summary information about manufacturing, and I will talk about what we mean by that in a few moments.

The CMC section -- again, some summary information. The changes in critical reagents have to be submitted in a PMA supplement. We're proposing manufacturers define what those critical reagents are so that, in conjunction with the guidance, we can let them

know when they need to come in, what's an important change that would require new review.

For PMAs we review final labeling; 510(k)s it's draft labeling. But the special controls will indicate what elements of the labels are necessary to be included going forward.

Because it's the same in a PMA and a 510(k), we are not going to be proposing much in the way of special controls for analytical performance, adverse reporting or post-market inspection, their software and instrumentation because those elements are reviewed similarly in PMAs and 510(k)s, so the reclassification would not affect those.

In the next couple of slides is a more detailed overview of the special controls that we are proposing, and finally I will touch on the detailed highlights. Basically, we have special controls that address the clinical samples that we are proposing be evaluated in the 510(k), the performance criteria for the primary studies, analytical samples that are necessary, how we are thinking about analytical performance criteria, and what we're doing with manufacturing. We have special controls that address reporting of complaints, and we have special controls that address the labeling.

We also have special controls that are designed for supplemental claims -- a subset of the general universe

of diagnostic claims. They have their own specific requirements -- for example, the types of samples that need to be tested -- and specific information that needs to be present in the labeling of supplemental devices.

Hitting the highlights, and again in the proposed order the exact wording of the special controls will be presented. But what we're talking about here is we are proposing specifying performance criteria and, of course, the clinical sensitivity and the clinical specificity lower bounds of 95 percent confidence intervals for point-of-care greater than or equal to 98 percent and, for the lab-based, greater than or equal to 98 percent, which is the same as what is present in the PMAs today and, as Anne presented, in all of the devices that have thus far been approved.

Because of the history of good performance of these devices we see no reason that one would want to decrease the performance of these devices and decrease those standards. Because all the other manufacturers have been able to meet these criteria we see no reason why, going forward, novel devices shouldn't need to meet those criteria as well.

This is also a case where, while we are specifying the performance criteria, we are not proposing to specify the number of samples that need to be tested to reach these criteria. This is an example of where we can be

flexible, and the reason is because the number of samples that need to be tested to reach a certain performance standard depends on the precision reproducibility of the device. Manufacturers, sponsors, are expected to pre-specify the number of samples they need to test. You can't just keep adding samples until you hit success, and that's because, during the development of the device they have expectations of how the device should be performing. So you can use those expectations, you can use your precision and reproducibility to calculate how many samples are going to be needed to meet these boundaries.

So you do the calculation, you pre-specify you're going to test 500 samples. If you can't meet it with this number of samples, you can't keep adding samples because what that means is your device is not performing the way you thought it was. And if it is not, you need to take a step back and try to understand why it's not performing the way you thought it was.

The number of samples necessary to meet this criterion can vary from device to device. However, it's also true you have seen the number of samples that have been historically tested that are necessary to show this. And while these are the lower bound of the 95 percent confidence interval, the point estimates, of course, are much, much higher.

While a new device doesn't have to be identical to a predicate, to be substantially equivalent it should be pretty close. If there are significant differences and we would want to understand why those differences occur. These are the lower bound performance criteria that we are proposing.

For some samples, however, they are very rare, for example Group O. If a manufacturer wants to include a Group O claim they have to validate that claim, but we are not going to tell them what the lower bound has to be because that wouldn't be reasonable. They would not be able to obtain enough samples in a reasonable amount of time to be able to actually reach those criteria. But we would be expecting them to be performing similarly to the other devices that have already been approved, which would be their predicate device, so we would look at that sort of thing and how they are performing.

We are proposing to specify the approximate number of samples that need to be tested for Group O for HIV-2, how those studies are. For supplemental devices, the manufacturers need to test for peak reactive/confirmed negative and confirmed indeterminate because those are the samples that are going to be evaluated by supplemental tests.

Similarly for the analytical, we are not specifying a sensitivity or specificity that must be achieved. However, we are proposing to specify within the special controls what the samples need to be tested for. And you will note that these are the same sample numbers and types that have been historically tested in all the PMAS.

Again, one expects a predicate device because it is substantially equivalent to be testing the same types of samples that were tested in -- well, a new device -- the same types of samples that are tested in the predicate, the PMA devices with predicate devices. And it has been demonstrated, based on the very good performance of these devices, that this kind of evaluation is necessary to maintain that performance.

What we don’t want to happen is a decrease in performance over time. We don’t want to have what can be considered predicate creep where, over time, they’re a little bit worse and a little bit worse and a little bit worse. If we specify these types of performance criteria and sample types we expect the performance to remain the same as it has been historically.

One other reason we’re not specifying, for example, sensitivity is because reagents evolve over time. Antibodies in the 1980s are not the antibodies that we

have now, and the same with NAT tests. Sensitivities can develop. We wouldn't want to set a criterion that's so high that everyone could comfortably meet it, even though over time the sensitivity of a NAT test, for example, drops tenfold.

We expect novel devices -- again, because you don't have the identical to a predicate -- a novel device can be more sensitive than the predicate -- we would expect it to be consistent with the current devices and with current technology as it exists at the time this is submitted. Remember, we're talking about going forward into the future so we don't know what's necessarily going to be out there. What we don't want to see is setting such a high level of sensitivity that novel devices are not doing what they ought to be able to do.

As I mentioned, there is no pre-approval inspection, so we're proposing that manufacturers submit some summary information on the manufacturing so that we can understand that the design controls and quality systems are in place when this device is put on the market. Here we are not talking about an entire CMC section, which is huge in a PMA. We're talking about summary information where manufacturers will define what are the critical reagents so it's understood up front both by the agency and by the sponsor that if they make a change, for example, in their

antibodies and their detection system, this is a critical change and they know up front how they are going to have to address that.

The device design verification summary, that it has been designed appropriately and that it is under control. The failure mode and effects analysis, that the manufacturers understand what can go wrong. We see a lot of things go wrong over the whole universe of devices that nobody would ever imagine could go wrong, so FDA has a perspective on what risks might occur that a manufacturer might have never encountered. We want to understand how they have been thinking about the risks and the impact of the risks and their device.

The lot release criteria, so we understand what their criteria are for putting things on the market. And the final release test results for three conformance lots. Again, this is because we are not doing an inspection but we want to know it is all in place and robust before we clear the new device.

We hope a lot of innovative devices come into the agency to meet the market needs.

Manufacturers determine what is an adverse event that rises to the level of potentially impacting patient safety, and those are reported as adverse events. But a lot of things happen that don’t rise to the level of affecting

patient safety and the manufacturer appropriately does not report those adverse events. However, you can get signals as to what's happening in a device, especially a novel device, if you can see what complaints are coming in over time.

For example, if you had controls that were spotty or not very consistent and that led to a high invalid rate and high retest rates, that is not going to hurt a patient because they're not getting any results, but if there's not enough sample or a patient is lost to care because there's a delay, that can have an impact going forward. There are other types of device class effects like the new impact of biotin on laboratory testing that was totally unanticipated by everybody but had a big effect on some devices.

The point is there are things that happen in devices that don't rise to the level of patient safety but FDA has a responsibility to understand what's happening with the --

(Fire alarm and short break)

DR. CALIENDO: We are going to resume where we left off.

DR. LATHROP: Fortunately, I don't have too much left here. I just want to make a couple of points about the special controls that we are proposing.

The report with the control logs will be submitted annually for the first five years after the initial clearance of the device. Changes that would need to be made that would merit, for example, a special 501(k) would not reset the clock. This is the first five years for a new device. It's separate from the adverse event reporting, and these complaint logs are not intended to be made public. I just wanted to clarify that.

Finally, we have special controls in place and I don't need to go through the details of all of these, but basically what they do is, because we review draft labeling and manufacturers can change labeling without coming into the FDA after clearance, we are proposing to include in the special controls requirements that the labeling has to contain certain elements.

These are elements that are already in the labels of the approved devices so there is nothing new, but we just want to make sure that they are in there going forward for the same reason that Anne said before, that the devices are used appropriately and interpreted correctly -- for example, especially the second one where, as novel issues arise -- for example, the biotin interference.

Or, this is a fast-evolving field and the implications and impact of PrEP on diagnostic testing is something of very great interest right now and how that

might affect. So, if devices appear to be impacted by PrEP, we would expect manufacturers to evaluate that effect on their device and update their labeling to reflect any impact that might be present.

There are restrictions that are specific to point-of-care devices that are in the labeling now. We propose to include special controls that would require those to continue to be in the labeling in the 510(k) devices going forward.

And there's labeling that is specific to supplemental claims. If it's a stand-alone supplemental claim it has to have a statement that says it is not a first-line diagnostic test. If it's just an addition to a diagnostic there's labeling that goes with that. And how to interpret the differentiation, because often it needs an algorithm to understand when everything is not quite clear how that should be interpreted and communicated to the patient.

Finally, just to reiterate again what we are asking from the panel. Now we have presented the risks and benefits of reclassification as FDA sees them, and what risks and benefits does the panel to see of reclassification. I have gone through the special controls, and again, the precise wording will be in the proposed order, so any discussion from the public or panel we will

get another chance to address those very specifically. I didn't want to go into the detailed wording here because it's very specific, regulatory language, but this is what we are trying to accomplish with these special controls.

If there are any special controls that maybe we have not addressed here that the panel would like us to consider -- and again, we are looking for general recommendations; we are not voting -- but recommendations on the special controls and on the concept of the reclassification. That is it.

DR. CALIENDO: Thank you, Julia. It's nice to know that you didn't lose your train of thought.

We lost about a half hour. We did get some sun so it wasn't like it was completely without benefit. But we are going to break for lunch now and come back at 12:30, like we were scheduled to do, so you will have about 50 minutes for lunch instead of an hour, and then we will use our discussion time after the public comment, so the public comment will be on time. Then we have the stretch of time for our discussion and we will have time at that point for questions for the FDA and discussion at the same time. It is my hope and expectation that we can still finish when we were scheduled to finish at 3:00 o'clock.

We will break for lunch. Committee members, please do not discuss the meeting topic during lunch

amongst yourselves or with any members of the audience. We will reconvene in this room at 12:30. I ask that all committee members please return on time. Audience members, please remember to take your belongings with you at this time. Thanks.

(Luncheon recess.)

AFTERNOON SESSION

Agenda Item: Open Public Hearing

DR. CALIENDO: We will now proceed with the open public hearing portion of the meeting. Public attendees are given an opportunity to address the panel to present data, information or views relevant to the meeting agenda. I will now read the open public hearing disclosure process statement.

Open public hearing conducted at a particular matter of general applicability. Welcome to the open public hearing session. Please state your name and your affiliation. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of advisory committee meetings, FDA believes it is important to understand the context of an individual’s presentation.

For this reason the FDA encourages you, the open public hearing speaker, as you begin, to state if you have any financial, personal or other professional relationships with any company or group or individual that might be affected by the topic of this meeting. If you do not have any such interest, FDA also encourages you to state that for the record. If you choose not to address this issue of financial, personal or other professional relationships at

the beginning of your statement, it will not preclude you from speaking and you may still give your comments.

Each of our open public hearing speakers will have five minutes, and we are going to start with Dr. Ann Gaynor. She is representing the Association of Public Health Laboratories.

DR. GAYNOR: Good afternoon. I am Anne Gaynor, I'm with the Association of Public Health Laboratories. I am the Manager of HIV, Viral Hepatitis, STD and TB Programs. I do not have any financial disclosures. We do, at the association, work with several federal partners including CDC and FDA, and we do have corporate members as members of the association so we do interact with corporate diagnostic manufacturers but have no financial interests.

The Association of Public Health Labs represents state and local governmental health laboratories that monitor and detect public health threats. APHL works to strengthen laboratory systems serving the public health in the U.S. and globally. Our mission is to shape national and global health outcomes by promoting the value and contributions of public health laboratories, and continuously improving the public health laboratory system and practice.

On behalf of the Association of Public Health Laboratories, please accept the following comments

concerning Docket No. FDA-2018-N0467, Joint Meeting of the Blood Products Advisory Committee. APHL supports the proposed reclassification of nucleic acid in serology-based point-of-care and laboratory-based in vitro diagnostics for use as aids in the diagnosis of human immunodeficiency virus.

APHL supports the reclassification of these viruses from Class III to Class II to achieve urgently needed improved accessibility to the latest HIV testing technologies in the United States. While quantitative nucleic acid tests for HIV were not included in the docket under consideration, APHL feels that these devices should not be excluded from the proposed reclassification from Class III to Class II.

Improving access to the state-of-the-art HIV tests will improve patient diagnosis, laboratory efficiency, patient management and public health surveillance. We believe that designating HIV diagnostic assays as Class II devices with general controls and potential special controls will be sufficient to provide reasonable assurance of the safety and efficacy of the assays.

The decision to regulate these devices under Class III controls was made decades ago when little hope could be offered to those who became infected with these

debilitating viruses. Diagnosis could equate to a death sentence. Since that time, we have made significant gains in our knowledge about these viruses and our ability to treat the infections they cause through research and epidemiological studies. This increased knowledge, including a vast amount of information on genetic variation in these viruses, has led to the creation of more robust tests.

The standards for validation of tests have evolved to ensure the diverse array of circulating genotypes and subtypes are detected. Additionally, the outcome of infection by these viruses has changed dramatically with the advent of highly effective antiretroviral therapies.

APHL believes that the reclassification to Class II devices for HIV would increase access to testing at a time when there is an increased incidence of both HCV and coincident HIV infection being driven by the opioid epidemic, and a strong need to identify infections earlier to prevent future transmission.

The reclassification could help with this by, one, decreasing the submission criteria submission criteria; two, shortening delays to market of newly developed assays; and three, increasing competition in the market. APHL contends that reclassification would not

increase the risk of adverse outcomes and safety and efficacy of assays.

One, APHL does not believe that down-classification would result in any adverse safety or efficacy outcomes. FDA down-classified Hepatitis A virus devices from Class III to Class II in 2006 with special controls and there have not been any adverse outcomes reported to date.

Diagnosis of HIV relies on a multi-step algorithm which, by design, mitigates risk. The potential risk from down-classification of a single device from Class III to Class II could be mitigated by the requirement of multiple devices being used to make the current diagnosis.

Two, currently there is virtually no competition in the diagnostic testing market for HIV-1 and 2 antibody differentiating tests, the second step in the recommended algorithm for HIV-1 nucleic or for HIV-1 nucleic acid amplification tests. Additionally, there is not a single FDA-approved diagnostic for HIV-2, as was mentioned this morning by Dr. Owen.

Down-classification of these devices as outlined previously could enable the development and quicker approval of additional devices. It would also increase the variety and types of assays available which would add to

the competition and better data on test effectiveness as well as the other devices to compare performance against.

Three, a decreased burden of submission criteria will reduce the size and cost of clinical trials as well as the cost of submission fees. Current 2018 standard user fees for medical devices are $300,000.00 greater for a PMA submission than a 510(k) submission. This is in addition to the additional cost of a clinical trial for PMA submission. This could incentivize current manufacturers to include additional specimen types; for example, drawing blood spots in the clinical trial design since it will be less costly to do so. This would also allow manufacturers with novel products to enter the arena when they have not been able to meet the burden of a PMA submission but have a valuable product.

A down-classification could shorten delays to market of newly developed HIV assays. Newly-developed assays typically receive a CE mark for testing and marketing in the European Union well before they are FDA approved. For example, the HIV-1/2 antigen-antibody combination assays were available in the European Union up to seven years before they were FDA approved for use in the United States.

Down-classification would, therefore, allow these tests that are capable of detecting HIV earlier in the

course of infection to reach the U.S. market in a shorter timeframe. This would in turn improve U.S. diagnostic capability to detect and diagnose these infections and thereby enable us to decrease transmission.

APHL partners with over 40 public health laboratories that follow the CDC-APHL HIV diagnostic algorithm and now have access to an HIV RNA test for HIV diagnosis are required to identify acute infections through two referral laboratories. The service enables these sites to access the diagnostic HIV test result, but turnaround time from sample question to net result is 12 days on average with only 80 percent of samples being tested within two weeks. Dr. Owen also mentioned this this morning.

This delay may result in additional transmissions. Increased commercial availability of diagnostic HIV RNA assays including simplified NATs with a diagnostic claim could significantly reduce this window.

We are at a time when the stringent requirements for a Class III device should be re-evaluated. Additionally, it should be known that even though these two viruses are under Class III controls, from an outside perspective it would seem that the HIV devices face an additional barrier compared to HCV devices with respect to obtaining approval from the FDA for diagnostic claims.

The evidence to support this apparent difference was the recent change in HCV nucleic acid tests where they were approved for dual claims for both diagnosis and monitoring; whereas, for HIV, this is not currently an option with the exclusion of quantitative HIV nucleic acids from this docket. APHL therefore suggests that FDA handle all devices within a classification with the same approach.

Lastly, this would also include ensuring that quantitative HIV nucleic acids for monitoring usage are also reclassified. This would obviate the need for the same test to be submitted twice due to discrepant controls required for the submission for a diagnostic assay versus a monitoring assay.

APHL believes the proposed reclassification, if adopted, will improve critical access to quality HIV tests and this in turn will improve patient diagnosis, laboratory efficiency, patient management and public health surveillance. In addition, it could significantly improve our ability to reach national goals of HIV elimination. This disease impacts disadvantaged populations disproportionately, and yet, all persons deserve access to the best diagnostics available.

Sincerely, Scott Becker, Executive Director, Association of Public Health Laboratories. Thank you.

DR. CALIENDO: Thank you. Our next speaker is Dr. Bernie Branson, representing Scientific Affairs, LLC.

DR. BRANSON: Thank you. My name is Dr. Bernard Branson. I am not receiving any commercial support for this testimony nor do I have any conflicts. I did serve as Associate Director for HIV Laboratory Diagnostics in the HIV Division at CDC until my retirement in 2014, and while there I interfaced with the FDA and the diagnostic industry to facilitate access to HIV testing technologies.

I have heard frequently from industry that a major barrier to seeking FDA approval for new devices or for incremental improvements was the onerous requirements for PMA and CBER regulations. In the background documents for this initial meeting, HCV and HIV, I found striking differences in FDA proposals for reclassifying HIV and HCV tests, two very similar groups of diagnostics.

These differences were illuminating and the approaches emblematic of the problem that industry faces as they seek approval for HIV tests, and especially multiplex tests like HIV/HCV or HIV/syphilis that, like HIV tests seeking CLIA waiver, require applications to two separate FDA centers. The CBER reclassification proposal suffers from some shortcomings not shared by the CDRH proposal for HCV tests, and I think that restricted HIV proposal will

perpetuate the regulatory hurdles that deny or delay access to cutting edge diagnostics in the United States.

I would like to make several suggestions.

All HIV in vitro diagnostic devices except those intended for blood screening should be reclassified to Class II, including all serological, NAT and viral load tests, as was recommended in March for HCV tests. HIV tests are not intrinsically high risk. At the 1999 meeting at which BPAC considered and classified the HIV genotypic resistance test as Class II, it was explained in some detail by FDA scientists that there are two reasons you get to be Class III. It's either life or death or there is no predicate, and the FDA can make Class II requirements as stringent as they want. And at that time, nearly 20 years ago, the HIV genotypic resistance test was labeled as a Class II.

The next consideration that I have some concern about is that FDA's use of sensitivity and specificity as performance standards for these tests with point estimates and confidence intervals here in Table 1 from your document is extremely misleading. If you look at the sensitivity results here, they estimate that the range of point estimates and the 95 percent confidence bounds don't go below 98 percent, and we all know that that is not true.

In the CDC study of 86,000 tests of 1300 HIV infections, only 87.5 percent were detected by the rapid test, only 97.7 percent were detected by the antigen-antibody immunoassay, and other studies show that oral fluid rapid test and other rapid tests have sensitivities as low as 80 percent. So, none of these tests, even when you compare sensitivity and specificity to presence of disease, come close to what the proposed requirement for the lower bound of the 95 percent confidence interval is.

The other thing the FDA table illustrates is the number of subjects that were required for clinical trials in order to achieve these somewhat high figures for sensitivity and specificity.

The mention of cost of over-regulation was conspicuously absent from the discussion. The user fees for a PMA application are $310,000. To make a change or supplement, the fee is $233,000. A 510(k) application price is $10,566. These are the 2018 user fees. The clinical trial requirement is between 4,000 and 11,000 specimens, and industry estimates it costs them to collect those at $1,000 apiece so that seeking an application or a change for a new test runs somewhere in the range of $5.5 million to $6 million.

The special controls specified in the background document would continue to impose these same stringent

requirements. The lower bound of the 95 percent confidence interval and the statistical power required to achieve this of 98 percent or 99 percent, the lower bound, is unrealistic as discussed at the March meeting at HCV. I think this should be harmonized with the CDRH proposal in general for the lower bound of the 95 percent confidence interval having a high point estimate but a lower bound of 95 percent.

I would like to talk about the issue of viral load and whether or not it should be part of this discussion and whether we need to reclassify it as Class II.

This illustrates the emergency department screening in nine hospitals across the country of 214,000 antigen-antibody combo tests. It identified 122 acute HIV infections. In that population, 9.6 percent of the qualitative map that’s available from resolution, but 2,865, or 93 percent, required RNA viral load for management.

I think the case for reclassifying viral load, there is sufficient information to determine that special controls are sufficient because of that predicate test to provide reasonable assurance of safety and effectiveness.

I know the committee can’t identify this. There are point-of-care nucleic acid tests that are available in

other jurisdictions in the European Union that are very much needed in the United States, and I'm wondering whether the question that could be considered at another committee meeting is whether diagnostic tests for HIV should be under the jurisdiction of CDRH and not CDER. Thank you very much.

DR. CALIENDO: Thank you. Our third speaker is Shek Smoak.

DR. SMOAK: I apologize for my bad script. It's Dr. Shelby Smoak. I am a professor, and you learn how to write terribly when you have all those papers to grade.

I am not sure if this is the right forum, but I have a concern and a question. Is this the time to present that, or is that later for questions for the committee?

DR. CALIENDO: No. This is the only time the public will have to comment.

DR. SMOAK: I am a patient. I have hemophilia, suffer from HIV and, thankfully, recently cleared Hep-C, so I have been attending your meetings and following them for some time. My question is based on some of the presentations that came earlier. I don't have anything formal to present.

My understanding is that individuals on PrEP taking Truvada are given a lifetime ban for donations. I wanted to see if I am confirmed in that. Also, based on that, I wondered in our screening if we were using evidence

of Truvada or evidence of PrEP in terms of how we screen patients for donations.

My last question from that is, it was also presented that there's a percentage of the population that develop resistance to these anti-retroviral therapies. Is there a potential possibility that in the donations maybe untruthful submissions are entering the plasma pool? Thank you.

DR. CALIENDO: Thank you. We are waiting to hear if FDA is open to commenting on this because that is not the topic of today's meeting.

DR. EDER: Dr. Smoak, thank you for your comments. This is not the forum to discuss them, but I can offer that blood centers have encountered donors who have volunteered that they are taking Truvada and they are being evaluated medically. So we are aware of the issue. I'm sorry we can't further discuss it here but we are aware of the issue.

Currently, blood centers manage the issue as it arises in their centers in evaluating donor eligibility.

DR. CALIENDO: Does anyone else in attendance wish to address the panel?

Okay. The public hearing section of the meeting is closed.

I think what we should do before we have the panel discussion is go back and open it up for the panel to

ask questions to the FDA speakers that we didn’t have time for before lunch. So let’s take some time, get your questions answered, and then we will move on to our deliberations.

Agenda Item: Questions for the Speakers

DR. DE MARIA: Al DeMaria, Massachusetts Department of Public Health. I thought the presentations this morning were very clear. I just have two questions to contextualize my thinking about this.

The first question is are there examples of PMA submissions for HIV diagnostic devices that were rejected? I guess I should ask how many were rejected, if any, if that is available.

DR. LATHROP: The FDA doesn’t comment on devices that have been submitted.

DR. DE MARIA: It would just give an idea of what the industry’s interest is in developing tests with predicates. We have heard a lot about it would be an advantage for reclassification. I think I am pretty much convinced that it makes sense to reclassify to Class II.

My question is how different is the handling of HIV diagnostic tests from all other similar circumstances? We heard just now that the Hepatitis-A diagnostic tests were down-classified in 2006. How does this compare to the general rule of what happens in these circumstances?

DR. LATHROP: The majority of infectious disease diagnostic tests are Class II devices right now. So, one of the reasons to bring this up at the moment along with HCV is that, with the accumulated experience, we think we can bring these devices into line with the classification of the majority of infectious disease devices. So we are moving to be more aligned in that way.

DR. DE MARIA: Is this something that has happened with other categories of devices? They have gone so long --

DR. LATHROP: Sure. HCV, for example, was recommended for reclassification in March. TB NAT devices were reclassified. This has happened before when the accumulated experience indicates that this is an appropriate thing to do.

DR. DE MARIA: It just seems like this should have happened a while ago. Is that fair to say?

DR. LATHROP: CMD devices, there was a meeting in 2016 for down-classification of those as well, so there is movement toward bringing them all into more consistent regulatory classification.

DR. PEEL: Sheila Peel, Department of Army. This is for you. I have concerns in the context that’s sort of aligned with Dr. Branson in the context of we were talking about predicate device comparison which had PMA extensive, multi-site clinical trials with thousands upon thousands,

sometimes 10,000 to 15,000, participants -- some of the newer devices which would actually fall in the de novo category probably.

I suspect these smaller manufacturers may, by default because of your special controls, actually be required to conduct very large trials that are economically not going to be possible, so I am really concerned about how stringent your lower bounds are.

I have been a clinical laboratorian for more years than I care to say, and I am going to be the last person on earth that wants degraded performance. But what we need now in the context of vaccine-induced seroreactivity, PrEP particularly, is to shift our diagnostic platforms to the left, to the eclipse phase and the RNA phase in a point-of-care or near point-of-care context, and I don't think those two things are equitable. I think you are going to lose what Europe has, right off the bat.

Number two, I have concerns about in your seroconversion panel requirements, most of those are decades old. They are hard to get, they're certified with predicate older assays, and the results of more sensitive tests are not going to be concordant. So you really need to think about what kind of serum conversion panels you're looking at and what their certification would be.

I know from my industry colleagues, they come to us a lot in the Army because we have quite an interesting set of panels and samples, but I am not a commercial entity so I can't share.

Lastly, your global panel, which here at the FDA is over 20 years old, the ECAPOL(phonetic) panel funded an NIH group of which my team is part is about to come online, but the accessibility of current circulating virus is a critical input into this, and there are not, to my knowledge, any plans to make that publicly available or funded by the U.S. government. I just wonder what your thoughts are on those.

DR. LATHROP: The criteria we're proposing now are keeping in line with the performance historically over all the devices, and the point-of-care 98 percent lower bound was recommended by BPAC in 2000, so that is also where that comes from.

What we have seen is, as we said, we have a history of excellent devices, very safe and very effective. What we don't want to have happen is through declassification any degradation of the performance of these devices. We are open to considering your comments. I think they are very valid and I appreciate them, but we are proposing at the moment -- Our key is to maintain the safety and performance of the devices.

And you are right. I think years ago the HIV diagnostic lab-based devices, the sensitivity and specificity were 10,000-sample studies, but BPAC then cut that back to 3,000 would be appropriate. And you can see from the bubble charts, a lot of the studies have gotten smaller because the devices have gotten better and are able to meet those bounds with fewer samples. So it is not necessarily the case that they would all require as large a study, but I am not sure. So we appreciate that feedback and take that into consideration.

As far as the seroconversion panels, the principle of the product kit is that it's substantially equivalent. In our experience with 510(k) devices, of which we have quite a lot, some of the predicates are very old, in other fields. They can be very old Class II devices. But the expectation is that the new sponsors will be using this state-of-the-art.

So, if there are newer panels that are more appropriate or the seroconversion, the historical data is not appropriate because in fact they are more sensitive now, the performance doesn't have to be the same. The principle is how are you going to look at real life sensitivity sero-converting a very low titer sample that's an actual clinical sample as opposed to just an artificial,

contrived sample. So seroconversion panels have been a way to get at that.

But we are always open to additional approaches if they are appropriate and get us the same information, and that is exactly the kind of thing we would encourage a sponsor to come in and talk to us about before they do it, if there's an alternate pathway they might be able to use that would get us the same information and would provide the same validation information.

DR. PEEL: I think you're going to have to. They are increasingly difficult to get your hands on --

DR. LATHROP: That's a very good point. The point there is that even though everyone has done seroconversion panels, what is the goal of the seroconversion panel. Like I said, to look at the sensitivity in a real clinical sample, which is not the same as a contrived sample. Which is why in the special controls we may consider alternate wording than just saying seroconversion panel, for example.

But the goal is to get that information, if there is another way it can be gotten that can be legitimate. So that is a very useful comment. I'm sorry, I don't remember your third one.

DR. PEEL: That's more your circulating global subtypes, recombinant circulating forms, CRS. I was just

making a comment that the panels that are generally available are two decades old.

DR. SPRING: Brad Spring with Becton Dickinson. Are there currently tests out there that have a dual intended use of viral load testing and diagnostic?

DR. LATHROP: I am not sure for HIV. I think there are for HCV. A single device could get that kind of claim for HIV.

DR. SPRING: Let’s assume there is. The follow-up question would be how would that be regulated if the diagnostic side has Class II and the viral load continues to have Class III?

DR. LATHROP: One thing we haven’t really had the opportunity to mention except in passing here is that while, as Anne said, we are not considering reclassification of viral load for monitoring today, that doesn’t mean that we can’t consider it almost immediately after today. And because of the comments and feedback that we have gotten from the panel and from the public, we don’t need to have another meeting in order to make that determination. We can take that information into consideration in our thoughts for viral load.

We decided to take an incremental approach when we started thinking about maybe this was the time for reclassification of the diagnostic. We have a very broad

range of diagnostic devices and with the CLIA-waived and the point-of-care and the supplemental, and we figured we would approach those first. But certainly, given the feedback we have had, we can consider that very quickly. It doesn’t have to start all over again years from now. But at the moment, they are not included in this.

In this proposed order if it were finalized, the viral load monitoring claim would be Class III. The same device could come in, though, for a diagnostic claim as a Class II, so you could have the same device with a Class III and a Class II claim. And if it was an already existing viral load device, the manufacturer should come and talk to us about what additional information would be necessary in order to get the diagnostic claim, but certainly if they have an existing viral load device come in for a Class II diagnostic claim. And they can co-exist. It is not an unusual situation at the FDA amongst IVDs.

DR. CALIENDO: We will go to Dr. Jones who is on the phone.

DR. JONES: Jefferson Jones, CDC. I was wondering if you could comment more on the comparison between HCV and HIV -- it was mentioned in the public comments -- given that we are trying to make things more standardized, reduce the stigma of HIV compared to other infections and possible

multiplex device, and the considerations of trying to make the special controls of HIV comparable to HCV.

The second question is, with some of the -- we talked about the large burden of multi-site studies that are mentioned in the special controls -- if using stored repository specimens would be acceptable to meet some of those large numbers or reducing the numbers. And related to that, the number for HIV-2 in particular seems difficult to obtain, that 200 number. Thank you.

DR. LATHROP: This was originally designed as a joint meeting between CDRH and CBER because we work very closely with CDRH and we have a very good and delightful relationship with them. When devices that are similar come in to the two, or a multiplex, for example, that might be regulated by both CDRH and CBER, we are in very close contact and communicate as to what we are looking for there.

As far as aligning the special controls with HCV the HIV proposed special controls, we are also working with them to bring them into alignment as much as we think is reasonable. A lot of the controls that are more general -- specific labeling requirements, submission of summary manufacturing information -- the decision was made to propose those for both types of devices.

The specific performance criteria that they're proposing versus what we are proposing are different. Our history with our devices is what leads us to believe that these sorts of criteria are necessary to make sure that we maintain their performance. Their devices are different and have a different history, and they are proposing criteria they feel are most appropriate for their devices. Two different devices, two different diseases. I am not ruling it out, but it does not necessarily follow that just because they are very similar that the special controls are going to be identical.

But we do communicate with them as much as possible. As we're finalizing the special controls for both of these and getting feedback, we will continue to be in communication with them.

As far as samples for clinical studies, we wanted to point out that in many cases repository samples are acceptable, so every study doesn't have to be a prospective clinical trial. Repository samples are often acceptable if they are well understood and the appropriate information can be gathered. That can help decrease the burden of having to go out and gather the appropriate samples for the validation of these devices.

DR. LEITMAN: Dr. Leitman, NIH clinical center. Dr. Lathrop, slide 10, performance criteria analytical,

where you list the analytical sensitivity samples, 200 worldwide samples, greater than 10 of this type -- there are a lot here. They are all available through FDA, through CDC. Is there an international collaboration on this? Where do those sample come from?

Dr. Peel just mentioned that they are two decades old. How could you have samples that have done so much -- if you used them for that many different purposes? What is the source of these samples?

DR. LATHROP: FDA does not provide the samples. FDA doesn't provide any samples for testing. I think CDC has some samples that they provide. We don't direct sponsors as to where they need to get their samples from, and it can vary from sponsor to sponsor.

DR. ALLEN: Same slide, Dr. Lathrop. Point b, the greater than or equal to 200 samples from patients with differential diagnoses, and then it gives HCV and HBV -- Is there a list of possible ones? Do you expect the manufacturers to identify them as they go through their tests? And is that 200 specimens for each one of these?

DR. LATHROP: No, it is not. It's 200 total. There is not a standard list; however, in the package inserts for all the different devices they list which differential diseases they do investigate, so that is public. And it's ones that are likely to be part of the differential

diagnosis of HIV. So, while there's not an absolute list, there's an expectation, for example, that HCV, HBV -- but it's 200 total, not 200 from each differential diagnosis.

For interfering substances, it's 100 samples from different interfering substances. There are endogenous interferences like hemoglobin, bilirubin, lipid, that are known to have a lot of interferences with IVDs. There may be other interferences that are specific to this particular disease that should be evaluated.

There are recent cases, for example, with biotin interference, which was a wholly unexpected situation. Normal ingestion of biotin through food or a multivitamins, manufacturers were evaluating interference there, 30 nanograms per ml, and reporting that in their package insert that they used that technology. But then consumer uptake has caused all kinds of problems with a lot of laboratory tests, so novel interference needs to be evaluated as well.

We don't always specify what they have to be. We expect the sponsors to be aware of what's going on and to address those. There are also typical ones that are looked at as well, and that's in all the package inserts and the summaries of safety and effectiveness data that are publicly available. So that information is easily accessible.

DR. CALIENDO: I have two thoughts. One is I am, too, concerned that with down-classifying, and if that's what the committee decides or suggests, are we fixing the problem? I look at the requirements that you put out there and they are very stringent, and in order to hit that sensitivity and specificity, I think these are going to continue to be very large studies. So I would just add my voice to the group of concern about is this going to fix the problem.

Two, help me understand how to reconcile your data, which is very compelling, and the data that Dr. Branson presented. Are we looking at what we often see in a clinical laboratory where clinical trials are done under ideal situations and all the perfect world, and what Dr. Branson showed us is the real world? I don't know. So help me understand your interpretation of those differences.

DR. LATHROP: Philosophically, it's true, and everyone knows that clinical study performance is as good as you're likely to get. Once they are in the clinic, there are all kinds of other interfering situations that can affect performance, although most of the time, most of these devices perform very closely to the data on which they were approved.

I think that keeping high standards for approval helps to ensure that you have the highest possible

performance in the clinic. I don't think lowering the standards is necessarily going to help improve the standards in the clinic.

Specifically for the data that Dr. Branson presented, in the Peters study with the 87.5 percent of the new diagnoses that were detected by the rapid test, that was a third-generation test which would not pick up the acute cases. The other cases that were detected were detected by antigen-antibody or a NAT test, and those are designed to pick up acute cases. So the additional diagnoses were acute cases that would not have been picked up in any situation by the third-generation assays. That is why there was only 87.5 percent sensitivity under those circumstances because that included acute cases.

DR. LEWIS: Roger Lewis, Harbor UCLA. I have a comment about the Chair's comment and then a question. They probably should be in the opposite order but I'm not going to do it that way.

The criteria defined by a limit on the lower bound of a 95 percent confidence interval does and does not require a specific sample size, because the observed performance peak can maximize at 100 percent. You can do a rough calculation and say that if you had 300 samples and every one was a true positive, the lower 95 percent limit on your confidence interval is going to be right at 99

percent. So 300 is the minimum number of samples you can do and make that. If you have one false negative and you still need your 95 percent confidence interval to beat 99, now you need a lot more samples.

The burden on the manufacturers in terms of just numbers of samples implied the lower limit of a confidence interval is very dependent on what the point estimate turns out to be. The more confident they are that they're not going to miss anything, the fewer samples they're going to need, so it actually builds in an incentive for better performance.

DR. CALIENDO: Or a bigger trial. As Julia said before, they are not allowed to add on at the end, so it kind of drives them to be more consistent or more conservative and have a bigger number to begin with.

DR. LEWIS: Yes. This is probably not a good place to get into a philosophical discussion about sequential testing algorithms, but I would be happy to after we are adjourned.

My question is about what's being asked of the committee. There's the broad question about whether or not we are comfortable with or would recommend the reclassification. Is that question asked only in the context of the specific special controls that are proposed, or are those separable questions where we can have an

opinion about the reclassification and an opinion about the controls?

DR. CALIENDO: If there aren't any more questions for Julia -- oh, there is one more. We will get to that. We will have them read the question to us again, but it's my understanding -- and Julia, please tell us if this is incorrect -- that you are open to thoughts on not just whether to down-classify but whether we would make any other additional comments regarding the special controls, whether you're missing controls or, in this case, it sounds like people want to comment on the stringency of the controls. And are there risks and benefits we haven't thought about. So we will go into all that when we deliberate. Is that correct?

DR. LATHROP: That is exactly right.

DR. CALIENDO: Does anyone have any more questions for anyone at the FDA? Okay, thank you very much. That was very helpful.

We are going to turn to Dr. Hobson now who will take us back to our question.

Agenda Item: Question for the Committee

DR. HOBSON: Real quickly, this is our proposal. I just want to highlight again that not included for today's discussion are the blood donor screening tests, the home use tests, viral load monitoring tests and phenotypic drug

resistance tests. As you heard other people discuss earlier, these are topics for another day and we would not necessarily have to have another meeting for potentially moving on things like viral load monitoring.

With that said, the question before the committee is: Do committee members believe that the special controls as described, in addition to general controls, are sufficient to mitigate the risks to health presented by reclassification of HIV serology and NAT point-of-care and laboratory-based diagnostic and supplemental devices?

This gets to the previous question. In addressing this question in the advisory committee, please discuss additional risks and/or special controls that we should consider.

I would like to turn it back over to Dr. Caliendo and I will listen to your deliberations. Thank you.

Agenda Item: Open Committee Discussion

DR. CALIENDO: Thank you. At this time, we are going to focus our discussion on the FDA question presented by Dr. Hobson. You have copies of the question in your folder.

I want to remind the panel that this is a deliberation period among the panel members only. Our task at hand is to answer their questions based on data, the presentations and the expertise around the table. With this

said, let's open the discussion. Please remember to identify yourself when you speak.

I will say that at the end of our discussion I will go around one at a time and specifically ask people to comment on whether or not they agree with the idea of down-classifying. This is not a formal vote, but I just want to give the FDA an understanding specifically of how everyone on this panel feels.

It is open now for discussion.

DR. LEWIS: I am going to continue the thought that I am now allowed to talk about.

It strikes me that the initial approach of simply taking the stringency of the criteria that were applied to the PMA process and copying it over to the Class II process is a very incremental and conservative approach. And given what seemed to me compelling arguments that we are trying to balance diagnostic accuracy against access to diagnosis -- because the test you never get is not very accurate -- I would hope that the agency would continue to re-evaluate the selection of the criteria in terms of the public health goals that they share with the CDC.

DR. SPRING: Brad Spring with Becton Dickenson. That's why I let Roger go first, because I just want to echo a number of the comments here. One of the major barriers to bringing these tests to market obviously is

cost, and that cost is embedded within the clinical trial for the most part. Yes, we do have high fees and things like that. That being said, we don't want to sacrifice or introduce new risk by using these tests.

But I think there is a balance between what I will call the real-world performance of these tests and the highly controlled, kind of perfect world performance, and that somewhere in between is a more acceptable, more in the point-of-care because we understand point-of-care may have some exceptional circumstances where these products are used that may introduce different types of error.

So, from a diagnostic standpoint I think, given the current special controls, the costs are still significantly high from a clinical trial standpoint.

But overall I do, obviously, agree with down-classification, and not just in bringing new tests to market but some of the barriers of improving existing tests, not just in performance but ease of use and other things. You know, things go wrong over time and it's harder to make these changes because you're spending a year sometimes waiting for that change to go through the FDA to then implement it, so there's a hesitation to actually make changes to existing products. I think down-classification alone helps in that area.

DR. CALIENDO: Thanks. We are going to go to Dr. Jones on the phone.

DR. JONES: I would like to echo some of the thoughts that have already been shared that support down-grading to Class II. I feel like a lot of the special controls are overly stringent and could harm -- could prevent us from what we are trying to do. Given the evidence that has been shared so far and the public health goals of having people aware of their infections and that treatment helps with prevention, that awareness of infection helps prevent further transmission, that the risk-benefit analysis of getting newer and better diagnostics unto the market, that would lead me to have less stringent special controls.

Some things that I kind of mentioned before -- to specify when stored that repository specimens can and cannot be used, that the current lower 95 percent confidence intervals for sensitivity and specificity seem to be overly stringent, the number of HIV-2 specimens would be very difficult to obtain, instead of 200 percent perhaps something lower such as 100 percent. I'll leave it at that for now.

DR. CALIENDO: Okay. Dr. Adeyemi is on the phone, also.

DR. ADEYEMI: This is Toyin Adeyemi. My comment is around the issue around increasing access and testing and looking at the table presented by Dr. Hardy and the populations that are actually remaining untested or needing to be linked. I support the down-classification, but again echoing what has been said about some of the stringency around what's required, and the HIV-2 comment that just came up. Again, those numbers will be really hard to reach.

And I am glad that the comment came up around some of the issues that we have discussed, that the viral load down-classification hopefully will be expedited because that is a big issue, especially around the fact that most of the new infections are actually in people who were prior diagnosed and are not engaged.

The last part of that is, also, as the CDC and NIH has endorsed U=U, it really becomes critically important that when people have lapses in their therapy to be able to rapidly assess if they are viremic when they are re-starting therapy so they know the timing of the U=U, the six months and things like that. So it does have implications as people have interruptions of therapy to have easier ways of assessing viremia in real time to counsel patients about risk of transmission.

DR. CALIENDO: Julia, I'm sorry, I had a question that I forgot to ask you. Can you help me understand? You

were talking about critical reagents and defining them. Is that something you do at the FDA, or is that something the manufacturer proposes to you?

DR. LATHROP: That is something the manufacturers propose, understanding it's their device and they know what's really critical to failure and where the edges of failure might be.

DR. CALIENDO: And if they neglected to include something like a primer or a probe or something that you thought was -- you would have the ability to influence that?

DR. LATHROP: We would have a question as to why they didn't include something that we would generally consider a critical reagent, and sometimes the answer is that we didn't understand and they were correct in what they did, and sometimes it's, yes, in fact, they ought to include that as well. They propose and then we respond.

DR. CALIENDO: I think the important point that Brad made is that down-classifying will allow companies to improve their tests. It is not uncommon to know that your test could be better and even to know what to do to make it better, but the burden to do that isn't worth the squeeze. That is one big advantage of this. It's not just the initial get-through, but then all the improvements that would follow from it. Thank you.

Questions? Is there anything that the FDA has missed in their special controls? Could we even imagine adding special controls? Now is your time to think about that. Okay, good.

Other risks or benefits? I think the comment that was made about balancing the risk and benefits is very important. I think our early speakers this morning did a very good job of helping us understand the clinical impact of not having these assays available.

DR. JONES: About the risk and benefits, I think getting the special controls as close to HCV as deemed possible would be preferable. We are also in full support of getting the viral load downgraded to Class II as soon as possible.

DR. CALIENDO: Anything else?

DR. SPRING: A question back to the FDA. One of the special controls -- I believe it was submission of product complaints over five years -- industry may have some concern about that around second-guessing how a company addresses certain complaints coming in, outside of adverse events, or even challenging whether something should have been an adverse event. What will the agency do with that kind of information? What kind of actions do you think the agency would take?

DR. LATHROP: Well, complaint logs are reviewed upon inspection anyway, so the agency has access to all that information periodically. Our concern is more that, for a novel device, if there were an issue that would have, upon inspection, required being addressed -- for example, a deficiency in CAPA procedures -- that would be addressed soon rather than waiting for the biennial inspection to come around.

I would expect that our response to that would be what it would be to any normal periodic review of complaint logs anyway. It wouldn't be introducing any new issues there. It's up to the manufacturers to determine what is reportable as an adverse event and they tell us why they believe that's appropriate, and we review that. So it's a sooner review but it's not introducing anything that we wouldn't normally have access to and respond to anyway.

DR. SPRING: Just a follow-up. The challenge to that is I think there are two different entities involved, though. One that goes in to inspect is more on the compliance side and may have more experience going into these sites and understands the complaints, versus say the premarket side looking at complaints and drawing different conclusions than maybe an auditor would. How would you address that potential conflict?

DR. LATHROP: Right now, when the field goes in to inspect, before they inspect they talk with the review divisions to see if there are any issues that we would like them to address that have raised questions, maybe some new safety signals. And when they come in and we would review them, and we would, as is customary, discuss with compliance if it was something. Before we take action we work with them to see their impression if they think this rises to the level of something.

So there's constant communication between the two offices, the premarket and post-market, so that we are responding appropriately. Because you're right, they have different experience looking at it and so they have a different perspective and that informs us.

DR. KAUFMAN: Richard Kaufman, Boston. I just have a question as to whether quality control, sort of QC that would go along with the normal use of these tests, either point-of-care or in the lab, falls under special controls.

DR. LATHROP: If the quality control materials, your positive/negative controls, things like that, internal control, is part of the device, it is reviewed as part of the device. Certainly, things like performance criteria do not apply. Quality control materials, if they are manufactured by the same manufacturer, would fall under

their quality systems regulations, so that is part of the device and would be reviewed in that context.

If it's sold separately as a quality control material and is not part of the device but is still part of the whole manufacturing and quality systems of the actual facility that does that work, in that context it would.

DR. KAUFMAN: Thank you.

DR. DE MARIA: In the absence of reflex diagnostic testing, I think most if not all clinicians in our state are going directly to viral load after seroconversion and a positive serologic test. If you did classify viral loads from III to II, how does that impact intended use indication for the test? It would have to be a separate process?

DR. LATHROP: In this proposal today, the quantitative viral load test indicated for monitoring is PMA, but we have talked about when we're going to reconsider that.

However, a quantitative viral load test that's used as an aid in diagnosis would fall under this proposal because they would now have an intended use as an aid in diagnosis. They would have to be validated for that purpose, and the scope of new information that that would require would depend on the individual test and what information was originally submitted to support it.

But those tests, used as a diagnostic -- which is a supplemental test as well -- that comes under the umbrella of diagnosis, which is then intended use population, and they would fall under this and would be submitted as a 510(k) if this proposal goes forward.

DR. CALIENDO: Any other comments, questions?

I would like to go around and get people's thoughts on whether you are in favor of the concept of down-classifying and then any other comments that you might have around the special controls or any comment that you want to make. Why don't we start with Dr. Adeyemi on the phone.

DR. ADEYEMI: Yes. I agree with the down-classification. I also still think that some of the confidence intervals and the stringency of the tests are high. I agree that the HIV-2 numbers need to probably be reduced, and I also would propose, while not part of this, that the HIV viral load testing be down-classified, as that will have a large impact on patients who are already diagnosed.

DR. JONES: I have nothing new to share. I agree with down-grading to Class II and, as previously shared, many of the current special controls are too stringent. Making them closer to HCV as much as possible would be preferred, and to really consider the public health

benefits of reducing the stringency, and doing the risk-benefit analysis of that would be beneficial.

DR. CALIENDO: What we will do, Dr. Baker, we will start with you and just go around.

DR. BAKER: I would also be in favor of down-classifying to Class II, being more flexible with the special controls as we previously discussed, bringing in the down-classification of the viral load testing as well. I think these would well serve our concerns on access to care and prevention.

DR. DE MARIA: I obviously agree with down-classifying from III to II. I am persuaded that the special controls are too stringent and too conservative in a number of areas, which it seems to me probably most likely is related to how long it took to down-classify this category of tests. And with all of the experience that has been presented and discussed and all the advantages, I think -- I'm looking forward to the public comments which I think will echo a lot of what we heard today. And I would definitely include the quantitative viral load monitoring tests.

DR. ESCOBAR: Miguel Escobar from University of Texas. I also agree with the downgrade classification as long as it is with the appropriate controls

DR. LEITMAN: Susan Leitman, NIH Clinical Center. I am strongly in favor of down-classification from Class III to Class II in view of the special controls described at this meeting.

I have a little difficulty with the stringency of the special controls because I come from a blood banking background. The stringency of the lower bounds for clinical sensitivity and specificity are just so critical to donor safety. This is patients, patient testing. I am just going to say I'm neutral on that and will just go by the expertise of the rest of the panel.

Three, sure, I agree that HIV viral load is critical as a part of both diagnostic testing and management, and I think strong consideration should be given to moving it from Class III to Class II.

DR. LEWIS: I also support the downgrading. I think the challenge with the stringency of the controls, as nicely illustrated by Dr. Leitman, is that it depends a lot on the setting in which the test is used, what the right balance is between access, speed and costs associated with innovation, and accuracy.

So, what I hope is that the agency has the flexibility moving forward to consider appropriate levels for the use in different settings and even consider that, for potentially settings in which we're trying to get

testing out into marginalized communities where access is critically important, the criteria might necessarily be different than in other diagnostic settings. And I just would hope that they would have some flexibility to think of that from the public health perspective.

I also agree that the quantitative viral load assays should be reconsidered and I am happy to hear that the agency can do that without asking us to travel again.

DR. SPRING: I agree as well on the reclassification or down-classification of both the diagnostic HIV as well as the supplemental tests. I would like to see viral load included in that. And I think we will have an opportunity through public comment to address the stringency of the special controls, so looking forward to that.

DR. BISHOPIC: I agree with the downgrading.

DR. PEEL: I concur as well, and I also want to echo Dr. Lewis' comments. I think they were very accurate in the context of the flexibility in terms of the intended use. That would be hugely powerful.

DR. SCHREIBER: Marty Schreiber, Oregon Health and Science University. I agree with downgrading and I have no additional comments in addition to the very nice comments made by my colleagues.

DR. KAUFMAN: Richard Kaufman, Brigham and Women's Hospital. I also strongly agree with down-classifying from III to II. I also think strong consideration should be given for the viral load testing.

DR. ALLEN: James Allen. After more than 30 years since the first licensure I think it's impressive, one, that progress has been made. It is time, certainly, for reclassification to Class II, and I strongly support that.

Dr. Lewis I think has raised some very good concerns, as have other speakers. It would be good to know for all of the current tests where they really stand in terms of sensitivity and specificity because, one, the quality of the test overall has improved dramatically.

On the other hand, we know that actual usage situations may make the actual usage or the actual sensitivity and specificity levels be quite different from what can be measured in a stringent laboratory setting. So we do need to be careful about that and make sure that clinicians and others using the tests are aware of the population-based aspects.

And, certainly, the level of infection that one expects to find in a population has a dramatic impact in terms of how the tests actually perform in those populations. I think at the appropriate time when the information is available, it makes great sense to

reclassify the other associated tests, and having a similar platform and type of specifications makes it much easier for the clinicians and people using it.

So I am very hopeful that the ingenuity of our manufacturing partners out there is going to provide some new and innovative tests, and I certainly think that the clinicians, based on information we have heard today, will rise to use it better to improve our public health.

In general, I would just say that I support -- I haven't read it carefully, but having gone quickly through the CDC document that was available to us today, the summary document, I would support their general approach.

DR. CALIENDO: I, too, support the down-classification which we have uniform support of. I think this has been a very interesting discussion. I think the whole idea of aligning it with Hepatitis-C is one that the group in general felt strongly about.

I like the idea of flexibility with regard to intended use and balancing the public health issues with the risks. That is not the easiest thing for you to do, but when I think of point-of-care, I think that's where the branch is. It's things that are used at point-of-care versus things that are used in the laboratory.

And when you listened to the speakers this morning, where a point-of-care test is going to be used is

really these high-risk populations that they are trying to reach, so it may be that you can work around that, the stringency issue, by having something different for point-of-care. You have it a little bit different but maybe making it a little more different on the point-of-care side. People don't do point-of-care at the beauty parlor where people are at no risk. They're bringing these tests to the patients in the community where they think they are at high risk, so I think there may be some flexibility there.

Many people spoke about the need to look at the number of HIV-2 specimens, the seroconversion panels, how hard those are, unusual strains. I would say that there are several viral load companies that do international surveillance, and so reaching out to them and seeing if they have a pool of unusual specimens that they could help other companies get these tests approved might be helpful.

I think using stored specimens is something that came up more than once and that is very important. It has helped certainly other microbiology and nucleic acid tests get through the FDA by being able to use stored specimens. The importance of allowing the company an easier way to improve a test is invaluable to us, clinically.

Finally, I think the group, everybody, totally agreed with bringing viral load assays along for the ride.

The comment that was made that I think is true is that the vast majority of laboratories that are doing RNA testing are using viral load because the one assay that's available that is approved isn't all that user-friendly, and you're bringing it in for a very low volume of testing. I think the reality is this is what we're doing anyway.

Is there anything else that we haven't addressed that you would like addressed, Julia?

DR. ALLEN: You reminded me of a point I wanted to make. Certainly, there might be repositories of samples including HIV-2 that are available. The red studies funded by NHLBI and conducted by many of our large blood banks in collaboration often with blood collection centers overseas probably have access to a number of specimens that might be made available at least in limited amounts for some of the studies here.

So, encouraging the investigators to go out and look for existing sources of specimens might be very helpful. This would include both viruses as well as serum specimens.

DR. CALIENDO: Okay. Last chance to speak your piece. Good.

I would like to thank the FDA for bringing this in front of us today and having the flexibility to

entertain us, and also the panel for your expertise and your engagement. Very much appreciated.

I pronounce the July 19, 2018 Blood Products Advisory Committee adjourned. Thank you very much.

MR. EMERY: I would like to say thank you to the public and to the participants from the FDA and on the panel for having a good discussion, and thank you for coming.

(Whereupon, at 1:50 p.m., the meeting was adjourned.)