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Center for Biologics Evaluation and Research (CBER)

117th Meeting of the Blood Products Advisory Committee

Joint Meeting with Microbiology Devices Panel of the Medical Devices Advisory Committee

March 22, 2018

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PROCEEDINGS (10:00 a.m.)

Agenda Item: Call to Order and Opening Remarks and Introduction of Committee

DR. CALIENDO: Good morning, everybody. I would like to call this meeting of the March 22nd, 2018 Joint Meeting with the Medical Devices Advisory Committee (Microbiology Devices Panel) and the Blood Products Advisory Committee to order. It is now 10:00 o'clock.

I am Angie Caliendo and I'm the Acting Chair of this panel. I am at Brown University where I practice infectious diseases in adults and also have an expertise in clinical microbiology. 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 from Class III to Class II of nucleic acid and serology-based *in vitro* diagnostic devices indicated for use as aids in the diagnosis of hepatitis-C infection and/or for use of aids in the management of hepatitis-C infected patients.

Before we begin I would like to ask our distinguished panel members and FDA staff seated at the

table to please introduce themselves. State your name, your area of expertise, your position and your affiliation.

DR. BAKER: Thank you. Judith Baker. My expertise is in public health. I serve as the Public Health Director for the Center for Inherited Blood Disorders in Orange County overseeing the Federal Hemophilia and Sickle Cell HRSA and CDC grants throughout the western U.S.

I am also an assistant professor in the School of Medicine at the University of California, Los Angeles.

DR. LEWIS: Good morning. I am Roger Lewis. I'm a professor and Chair of Emergency Medicine at Harvard UCLA Medical Center. My expertise is in clinical emergency medicine, research design and clinical trial statistics.

DR. ORTEL: I am Tom Ortel from Duke. I'm a professor of medicine in pathology, I am Chief of the Division of Hematology, and I'm also the Director of the Coagulation Laboratory at Duke. My interest is in hemostasis, thrombosis and testing for these conditions.

DR. REES: Good morning, I am Robert Reese. I'm the Manager of the New Jersey State Department of Health Blood Bank Regulatory and Compliance Program. That is my primary area of expertise. I am more involved with the blood bank and donor blood regulation and licensing.

DR. SANDBERG: Good morning. I am Sonja Sandberg. I am a math professor at Framingham State University, and my area of expertise is risk assessment.

DR. STAPLETON: I am Jack Stapleton, professor of medicine and microbiology at University of Iowa. My clinical interests are HIV and hep-C and my research interests are flaviviruses and hep-C.

DR. SPRING: I am Brad Spring. I'm the Vice President of Regulatory Affairs at Becton Dickinson and Company in the Life Sciences Segment, and I am the industry representative for the Microbiology Devices Panel.

DR. SCHERF: Good morning. My name is Uwe Scherf. I am the Director of the Division of Microbiology Devices of the FDA. My expertise is evaluation and clinical approval of *in vitro* diagnostics for infectious diseases.

DR. GITTERMAN: My name is Steve Gitterman. I am Deputy Director of the Division of Microbiology Devices at CDRH, and my expertise is in infectious diseases.

DR. WARD: Good morning. I am Dr. John Ward. I am with the Centers for Disease Control and Prevention. My area of expertise is viral hepatitis and the prevention of viral hepatitis. In our division we are responsible for -- relevant to this conversation -- testing guidelines for the

United States and have a reference lab for the United States which you will be hearing from in a moment.

Currently, I am with the Task Force for Global Health helping them develop a viral hepatitis elimination program, and I have a professorship in the Rollins School of Public Health at Emory University.

DR. THOMAS: I am Dave Thomas. I'm a professor of medicine from Johns Hopkins in Baltimore, and I am an infectious disease clinician who has an interest in HIV and hepatitis-C.

DR. ADEYEMI: Toyin Adeyemi, associate professor of medicine at Rush Medical College at Chicago and infectious disease at Cook County Hospital. I direct the viral hepatitis program and my areas of interest include hepatitis and HIV and aging.

DR. MILLER: Good morning. I'm Melissa Miller. I am professor of pathology and laboratory medicine at UNC Chapel Hill. My expertise is clinical microbiology, and I am the Director of Molecular Microbiology for the healthcare system at UNC and Associate Director for Microbiology and Immunology.

DR. KIMBERLIN: I am David Kimberlin, pediatric infectious disease, professor of pediatrics, University of Alabama at Birmingham. My areas of interest are perinatal

and congenital infections, antiviral therapies and trial design.

DR. DODD: I am Lori Dodd from the National Institute of Allergy and Infectious Diseases. I am a biostatistician with interests including clinical trials and the statistical evaluation of diagnostic tests.

DR. CALIENDO: Thank you, everybody. If you haven’t done so already, please sign the attendance sheets that are on the tables by the door. LCDR Bryan Emery, the designated federal officer for this meeting, is going to make some introductory comments.

LCDR. EMERY: Good morning. Before I do the introductory remarks, we have people on the phone who are also attending who are panel members who were not able to come due to inclement weather. One is having technical difficulties getting on, but I believe one is still on at this time. Dr. DeMaria, can you introduce yourself?

DR. DE MARIA: Good morning. It’s Al DeMaria. I am the Medical Director, Bureau of Infectious Disease and Laboratory Sciences at the Massachusetts Department of Public Health and the Massachusetts State Epidemiologist. My areas of expertise are infectious disease and epidemiology.

LCDR. EMERY: Also, be sure to mute your phone while you are attending until we have you speak, just because we won't have the ability to control it on this end.

Patricia, are you on? We will have Patricia Lupole, the patient representative, announce herself when we have her on the line. Now I will begin with my statement.

CBER deeply regrets having to cancel yesterday's panel meeting due to the weather for the inconvenience caused to the committee members and to the public. We intend to proceed with a public discussion of HIV reclassification at a future date. The date will be announced in the Federal Register and on the CBER website.

Good morning. I am Bryan Emery, the designated federal official for today's meeting of the Blood Products Advisory Committee. Mrs. Joanne Lipkind and Mrs. Joyce Mercer-Dickens are the Committee Management Specialists and they will assist with your needs at the tables located in the hall.

I would also like to welcome all of you today to the 117th 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 and media contact is Mrs. Megan McSeveney. Our transcriptionist is Chanda Chhay.

I would like to request that everyone please check your cell phones and pagers to make sure they are turned off or in 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 outside the doors to the right located at the kiosk down the hall. The rest rooms are also there. Remember to pay at the kiosk for your lunch and the lunch will be provided to you at the back of the kiosk when we break for lunch later this afternoon.

All committee topic discussion needs to be done in a 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.

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

Agenda Item: Conflict of Interest Statement

LCDR EMERY: The Food and Drug Administration is convening today its Joint Meeting of the Blood Products Advisory Committee and the Microbiology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict-of-interest laws and regulations.

The following information on the status of this joint committee's compliance with federal ethics and conflict-of-interest laws covered by, but not limited to, those found at USC 208 are being provided to participants in today's meeting and to the public. FDA has determined that members and consultants of this Joint Committee are in compliance with federal ethics and conflict-of-interest laws under 18 USC 208.

Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have financial conflicts when it is determined that the agency's need for the particular individual's services

outweighs his or her potential financial conflict of interest related to the discussion of today's meeting.

Members and consultants of this joint meeting who are special government employees or regular federal employees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 USC 208, their employers. These interests may include consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

For today's agenda, the joint committee will discuss and make recommendations regarding the reclassification from Class III to Class II of nucleic acid and serology-based *in vitro* diagnostic devices indicated for use as aids in the diagnosis of hepatitis-C virus, infection, and/or for use as aids in the management of HCV-infected patients. All the devices that will be discussed by the committee during the meeting are post-amendment devices that currently are classified into Class III under Section 513(f)(1) of the Federal Food, Drug and Cosmetic Act, 21 USC 360.

Based on the agenda for today's meeting and all financial interests reported by the joint committee members and consultants, no conflict-of-interest waivers have been issued in accordance with 18 USC 208.

Mr. Bradford Spring is serving as the acting industry representative. He brings industry perspective on behalf of all related industry and is employed by Becton Dickinson. Industry representatives are not special government employees and they do not participate in the closed sessions and do not have voting privileges.

Dr. Judith Baker is serving as the consumer representative and brings consumer perspective to the committee deliberations. Consumer representatives are appointed as special government employees. Today, the advisory committee will be seated as a device panel and the consumer representative will not vote.

Dr. Patricia Lupole is serving as our patient representative for this topic. She brings valuable patient perspective to the committee deliberations on this topic.

We would like to recommend to members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from

such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the joint committee of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and it will be included as part of the official transcript.

I would also like to let the audience know that there were four written statements that were sent in which are posted also in the viewing binder that is at the table if you want to see them.

At this time, I will turn it back to Dr. Caliendo.

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

DR. DE VAN: I'm Michael DeVan. I am Medical Director at Transfusion Services at Walter Reed and Deputy Director for Clinical Support there.

DR. CALIENDO: We are going to start with our presentations. I will note that the plan right now is that we are going to go through Dr. Garcia's presentation and then break for lunch, so there will be no morning break since we got started so late, and then we will pick up the

Agenda from there in the afternoon. We are going to start with Dr. Scherf.

Topic III: Device Reclassification from Class III to Class II of Nucleic Acid and Serology-Based *in vitro* Diagnostic Devices Indicated for Use as Aids in the Diagnosis of Hepatitis C Virus (HCV) Infection and/or for Use of Aids in the Management of HCV Infected Patients

Agenda Item: Introduction to Topic and Welcome

DR. SCHERF: My name is Uwe Scherf. I am the Division Director of the Division of Microbiology Devices in the Office of *In Vitro* Diagnostic and Radiological Health. You already the information on the housekeeping so I will not repeat that. I would like to welcome you all to Washington, D.C., especially the members, the speakers and the attendants of this initially planned joint meeting between CBER and CDRH. You can imagine we did not plan it like this. We wanted to have a meeting that would be remembered but not due to the weather. We wanted to have it remembered due to our scientific and regulatory accomplishments today, but I am confident we will still be able to accomplish that.

I would also like to thank the speakers and the panel members for their public service and their contributions basically to this panel meeting. For us, it

is a clear service to FDA and we really much appreciate that from your side.

Also, the panel meetings represent an important part of FDA's deliberations as we move forward with different devices, and these challenges will be addressed by you, which will support our work here at FDA. Please recognize that we will make your advice to this panel part of our decision, and we very much appreciate all of the feedback that you will provide to us today.

FDA has two missions. Most people know the first one, to protect public health, and we do this by reviewing, in our case, the devices before the end of the market and the pre-market environment and after they are introduced into the market. But there is also a second mission that we have, and that is to promote public health, and that is what we are planning to do today.

FDA, on its own initiative, has convened this panel meeting, as we did for the discussion of CMV and EBV viral load assays two years ago. We are proposing the reclassification of HCV tests from Class III to Class II. We believe it is time to have the benefit-risk discussions about HCV diagnostics and to discuss how identified risks can be mitigated properly.

My colleagues, Dr. Garcia, Dr. Schlottmann and Dr. Gitterman, will describe in detail in their presentations the issues, but what I would like to do is to start you thinking about some of the concepts that actually are essential for making decisions on whether you can down-classify something. There are two concepts that I would like to share with you.

The first one is really the question can a Class III device be evaluated, and can the risks be determined. The next question, of course, after we determine the risks, is can they be mitigated. The second issue would be, if the risks are determined, can they also then be described via special controls. Only under these two conditions will we be able to move forward and down-classify a device from Class III to Class II, and the following presentations will in detail describe these approaches.

The goal of the meeting is we would like to have a discussion of the reclassification of serological-based nucleic acid-based HCV tests currently regulated as Class III, into Class II, and we would like to obtain the panel's assessment of whether the risks using the serological and nucleic acid-based HCV tests can be mitigated with special controls.

The morning agenda has been changed a little bit. The morning will describe the HCV diagnostics and the concepts I just described, and in the afternoon we will address and we will support the open public hearing and we will discuss the questions from FDA to the panel and have deliberation.

Finally, I would like to thank the panel committee. Again, this meeting was extraordinary, and a lot of people put a lot of work in yesterday to still make this panel happen and I would like to thank them all. It was quite a long day.

We have an outstanding agenda. It is tight, but I would like to, again, thank some of my colleagues because I am not sure whether later in the day there will be enough time to do so. I would like to thank Dr. Garcia, Dr. Schlottmann, Dr. Gitterman and the staff of the Microbiology Devices Division who helped with putting this meeting together. The lawyers of ORR, Mr. Ryan Lubert and Scott McFarland, as well as Office Director Don Sempiere, the CDRH and CBER advisory committee staff, especially LCDR Bryan Emery, James Swing, Aden Asef, our invited speakers, Dr. Kamili and Dr. Kim.

This concludes my introduction. Again, I would like to thank you for your public service, and I give the floor back to Dr. Caliendo.

DR. CALIENDO: Thank you. We are going to have three speakers and then we will have a break for questions. The next speaker is Dr. Gitterman.

Agenda Item: Reclassification Process Overview

DR. GITTERMAN: Again, I would like to thank the committee. Due to the abridged schedule I am going to be very quick, so think of this as the notes you write on your Cliff notes, and we will dispense with the pretest and the post-test so I will not know if you have achieved the objectives.

This is, again, very, very abridged, but basically, device classification is three classes: Class I, things that you would not think twice about, swabs, things like that, things that FDA regulates but are generally exempt which means you don’t have to submit anything to FDA; you just have to notify us that you are marketing it, but you have to commit and follow general controls. I will describe them in a minute.

Class II has a moderate likelihood of harm or risk. This is probably a majority of what you would do in a clinical laboratory environment. Some people may argue with

it but it's a generalization, and these require a 510K, named after the section of the Act where this is specified. The difference between this and Class I from a regulatory perspective, despite the 10,000 things I am leaving out, is, in fact, that you need special controls. The general controls don't cut it in this case. You need additional special controls unique to that device class and that regulation. It is also the case that you can submit less information to the FDA. It requires a 510K submission, and less is always relative. That will be relative to the PMA which is Class III.

Class III is high or unknown risk of harm, and they are generally considered very significant-risk devices. But also, by the same token, they are devices for which we do not believe we could write special controls. It is uncertain enough that each application has to be looked at individually, and that's called the PMA which requires premarket approval, and that is burdensome, or at least we are told -- or perhaps Mr. Spring could comment later -- that it's burdensome to industry. But it requires the most review and the most information submitted -- I will make a distinction there later -- to FDA.

Here again is basically the same slide in pictorial form. Class I is low risk; Class II is moderate

risk; Class III is high risk. The controls are general for Class I, general plus special for Class II, and general plus clinical validity for Class III. Under studies submitted, you don't have to submit to FDA for Class I. Class II and Class III there will be analytical and clinical studies.

I will mention *de novo*. If you look very carefully at the last slide, under Class II you can see *de novo*. Basically, what the law states is that if there is no predicate for a device -- Well, Class II means a device of that class has been cleared previously. FDA has reviewed it for devices for *in vitro* diagnostics, and it is called cleared.

Any new device that comes in is, by default, a Class III because it doesn't have a predicate and we have unknown risk of harm. As you can imagine, that would be very burdensome requiring industry, if you came with just something, a new analyte that had not previously been sent to FDA, to put in a new PMA. I know these concepts are still fuzzy, but Dr. Garcia is going to go over them again. Repetition is good. We have a process called the *de novo* process, where you can come in and basically be granted a *de novo*, which is roughly equivalent to a Class II submission.

So, again, even if we not seen a device before, it does not necessarily have to be in the most, quote, “burdensome” requirement which is Class III. But, of course, Class III also gives us the most oversight and is appropriate for a number of devices.

What is the difference between a Class II and a Class III submission? Again, it is very similar -- Class II and Class I, again, one of those distinctions I didn’t make in the need for time, but some Class I devices do come into FDA that we review, but relatively few. But this is substantially equivalent. They have to be equivalent to a device that has been marketed previously for the same use, may require clinical studies, needs internal documentation of adherence. That means the companies have to do the studies; they just don’t have to send them to FDA to review. The software instrumentation requirements are the same, and the labeling -- we review draft labeling but we don’t see the final labeling.

For a PMA they have to demonstrate safety and effectiveness. They have to almost always require clinical studies, and that is almost. There are notable exceptions. It is reviewed with the submission, and we review final labeling as well as changes to labeling.

I know I;m going quickly and I apologize. One reasons that’s underlined is these are the differences in the slide between submissions, what they send to FDA for a marketing application. That does not describe what they do after you are on the market. This is basically at the time you have developed a product and you want to market it, what FDA will review. I am going to make that distinction again later.

There are some other similarities and differences. They both get post-market inspections, adverse event reportings. We treat each device, regardless of the class, by the least burdensome approach. There is no pre-clearance inspection but there is an inspection for Class III. This is cleared by the 510K. This is PMA supplements.

And this particular one is sort of post-marketing. If you change something critical in your device, there’s a guidance which specifies that, if there are significant changes, a new 510K is required. A PMA supplement is always required if there’s a change to the device. There is a little more oversight in the Class III PMA approach than there is the 510K approach.

The other aspect is, since we are getting more information and more actual documents submitted our

obligation is higher, and we have a longer regulatory time clock for the PMA submission.

What are the differences between general and special controls? I referred to this three slides ago, Remember, Class I, Class II and Class III all have general controls. General controls are all you need for Class I. Class II has special controls. One major difference is general controls are general and special controls are special. That is not a joke, although I did get a smile there.

The special controls are specific to that device class. If you are developing device X, and for device X to be used safely you need something that goes beyond general controls, you need special controls. The difference is that special controls are those things you do in addition to general controls for a specific device class.

General controls apply to all devices. These are some examples. You cannot adulterate your product or you can’t misbrand it, of course. You have to follow the quality systems regulation, good manufacturing process. You have to send your intent to register and list it, and you are still obligated to report adverse events. There are other things. Again, this is the Cliff notes view.

For special controls there are device-specific requirements. All devices that are under a regulation that is not Class I-exempt will have these. These may include but are not limited to performance standards, post-marketing surveillance, premarket data and special labeling requirements. By premarket data, it's the nature of the data you need to send in, because, again, for specific devices -- for a TB device you may have certain needs that you would not have for another type of device. And they must be followed. It's the law. The special controls are the law for that regulation. Or, if FDA's intent is to not enforce the regulation, then a new regulation will be necessary.

So, what is reclassification? It is allowed under the FD&C Act; we can do it. We are not asking you to do anything illegal. It is initiated by FDA. It's based on experience with devices and new information about risks and mitigations. Reclassification can go up or down. You don't have to worry about going up; we're talking about reclassification down. Basically, FDA has an obligation to appropriately classify every device.

If we think enough information has evolved or has been published or, for whatever reason, has accumulated, we can reclassify a device from Class III to Class II. That

has advantages to industry in a lot of ways. It does not lower the bar; it lowers the regulatory requirements in some ways for submission to FDA. But it does have benefits to industry and it does foster innovation in some ways.

Again, we have to have sufficient information to write special controls. If we can't write down what we want sponsors to do then there has to be a PMA. We have to customize it for every application.

And, of course, the point of special controls is to provide a reasonable assurance of safety and effectiveness.

This is what the meeting is about today. This, in essence, these three points, are what we are talking about today. Does the committee concur that, with special controls, -- I don't mean concur with me, but concur with the statement -- all or some of the HCV devices discussed today can be reclassified as Class II? That is the bottom line. The essay question on the test is this one.

I would like to thank Julia Lathrop. If you go through your packet you will see many of these slides were stolen. I had to re-jigger my slides because Julia was giving you an excellent half-hour talk on this yesterday and you probably didn't get to hear it. None of us did.

I have one minute for questions. Brad, can you concur with the point about Class III and Class II?

MR. SPRING: Yes, I concur, and will maybe hold my questions for the special controls that you propose for later because they do appear to be different than what the table has up there -- 510K versus PMA.

DR. GITTERMAN: Thank you.

DR. KIMBERLIN: Can you further delineate how *de novo* versus Class III would be distinguished? Is it something where FDA says this can come in as *de novo* or is it selected by the company?

DR. GITTERMAN: I only put *de novo* in just for completeness. It is not applicable to the meeting today.

For new devices -- let’s say you came out with a *de novo* for X virus which was discovered. That would be a *de novo* as we have never cleared a device for X virus. And you would be surprised how many common diseases actually do not have a cleared FDA product. So it would be basically something that we don’t want to make Class III when it comes in because that would be incredibly burdensome to industry, It’s a way for us to basically make a device a Class II even though there is no predicate or precedent.

Thank you very much.

DR. CALIENDO: Thank you, Dr. Gitterman.

Our next speaker is Dr. Kim from Harvard Medical School and he is going to be talking about testing for hepatitis-C virus, a clinician's perspective.

Agenda Item: Testing for Hepatitis C Virus: A Clinician's Perspective

DR. KIM: Thank you for the introduction, and thank you to Steve for finding me to give this talk. This is my first visit to the FDA so I am excited to be here. I tried to escape Boston's snowstorms but unfortunately they seem to be here as well.

These are disclosures. If I happen to mention resistance testing or core antigen testing, these are not approved tests at present.

By way of background, I don't want to review all of hepatitis-C in multiple slides, but I think everyone in the room is aware that hepatitis-C is a major challenge to public health, is a frequent infection that's a leading cause of morbidity and mortality on the average associated with 20 years of lost life expectancy if positive, and transmission, and most of the natural history is often silent. Given those needs and the situation clinically and from a public health standpoint, there remain some unmet needs in testing for hepatitis-C.

The next slide goes over the WHO or Wilson criteria for what's described as a good screening test. I just described how the condition is an important health problem. Indeed, hepatitis-C kills more people than 59 other infectious diseases combined, per the CDC. There should be a treatment for the condition, and there are novel treatments in hepatitis-C that now allow cure for the vast majority of individuals, and, in fact, along with certain cancer therapeutics one would describe this as one of two major therapeutic revolutions in recent years.

Diagnosis and treatment facilities should be available, which they generally are in most places. There should be a latent stage of the disease. This is clear in hepatitis-C where long latent periods, 20 to 30 to 40 years, occur before the end results of cirrhosis and the primary threats to mortality associated with this disease and infection.

There should be a test, and we will hear in the next talk more specifics about these tests, and I will allude to this. There are very well-established tests for this condition.

Tests should be acceptable. Blood testing is generally considered acceptable.

The natural history of the disease should be adequately understood, and thanks to certain people in the room such as Dave Thomas, we do understand this disease quite well, what modulates the course of the disease, what accelerates the course, what delays the course, et cetera.

There should be an agreed-upon policy on whom to treat. At least the major societies, such as the Liver Disease Society as well as the Infectious Disease Society, have convened to provide these guidelines. In general, they would state that anyone harboring this infection should be treated to prevent those downstream complications.

The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole. I guess it’s a fancy way to talk about cost-effectiveness. Recently, there was even a paper describing that general screening of the population, of the entire U.S. adult population, would be cost-effective relative to other medical interventions.

And finally, case finding should be a continuous process. Simply stated, hepatitis-C clearly qualifies as a screening test that should be applied broadly, et cetera.

There are other versions of the algorithm for diagnosis which will be reviewed in more detail in the next slide, but there has been this situation of two-stage

testing for hepatitis-C for quite some time where one begins with the antibody -- again, a review I know for many in the room -- but if non-reactive, then without antibody detection generally we stop testing. There are people who continue to be at risk for hepatitis-C infection, and so it is not a true stop there for those individuals who have ongoing risk factors.

If reactive, it stays generally reactive for the individual's lifetime, and the next step would be the hepatitis RNA test or nucleic acid test for the RNA in the blood. If not detected, that suggests no current hepatitis-C infection. That could be accomplished either from spontaneous clearance, -- which I will describe in a future slide -- from treatment-induced clearance -- it gets to that point as well -- as well as potentially false positive testing.

Again, additional testing may be required at that point if the patient has ongoing risks, and that generally needs to be accomplished by hepatitis-C RNA as the antibody is already positive. If detected, which is the middle graph, one can describe current hepatitis-C infection and then link them to care.

Now, there are multiple tests available described in the next talk. These are excellent tests with high

specificities and sensitivities. Blood tests and now rapid tests have become available. The cost differential between the antibody and the RNA actually is the reason why we have this two-stage testing. Why not just cut to the chase and test for current hepatitis-C infection? So, if there were ways to lower the cost one could simplify this diagnostic algorithm.

Again, describing this from at least my perspective to talk about both antibody and molecular testing, the pros of the antibody is that it also captures exposure. If we were to skip directly to current infection, those who may have spontaneously cleared, that is still a marker of where exposures and infections are occurring potentially, even if they are spontaneously clearing their infection. And so, from perhaps a public health perspective that still can be useful, or from a personal health perspective if they encountered a patient and they cleared, it’s a marker that there was some risk before that could then be mitigated in the future for prevention, et cetera. As mentioned, it is cheaper.

The cons are, well, hepatitis-C antibody, as it is the first step in every algorithm and as patients present to different systems and whatnot, once positive it’s repeated unnecessarily over and over and over again.

For instance, you could take a patient who presents to an emergency room and they are tested, and then they present to a different emergency room and they are tested again. If you follow this -- Al DeMaria who is on the phone in our state probably sees this, where an individual could receive, once positive, 20 tests afterwards in different settings. They go to prison; they need an antibody to initiate the process yet again, and even policies are in place so you cannot rely on a test that you can't see. If we had integrated medical information systems, that could abrogate that.

The sero-negative window -- There is a brief period of infection that lasts for weeks or up to months where patients can be viremic and infected and the antibody is negative.

Incorrect interpretation -- Patients and providers are often told with the antibody, hey, you have hepatitis-C, and they come in panicked because they have learned incorrectly that they have hepatitis-C. That can be true and false positives, spontaneous clearance, et cetera. This situation has resulted in one of the major arguments against expanded testing, which is stigma associated with that type of antibody test, because in the end, if you are clear and you have no ongoing risk, there's not much more

that we do for that patient and yet you have informed them about something that can be disconcerting.

Molecular testing is vital to confirm active infection and then afterwards to confirm clearance and cure. It's more expensive than antibody testing, and, therefore, it is generally not first line for identification of infection.

And, unlike HIV viral load, it is important to state that it's a poor correlate for future fibrosis. If it's high or if it's mid-range or whatnot, one can still have similar disease progression.

I'll be talking about the sero-negative window in a little bit more detail. In this case, the antibodies are rising after the RNA appears first, the stylized ALT activity spike, which can be marked and can present in the thousands or can be not so marked and present in just double digits.

After this transmission, which is generally silent, there is this window where, if you identify a patient with acute hepatitis-C or risk factors for it, then perhaps one would look for that active infection beforehand. After spontaneous clearance, we have described the scenario where patients are antibody-positive and RNA-negative, and their ALT tends to normalize. And here we see

the usual case in the majority of individuals who are exposed and infected where the antibodies kind of look the same, but then there is an infection that persists for the host's lifetime until treated. There can be ALT abnormalities, although, in up to 20 percent of people those can remain in normal range. Thus, ALT is not considered a good screening test for this infection. Again, antibody does not equal current infection, and that's the situation that we are in clinically.

To talk about acute hepatitis-C and why it's important -- many of us have been thinking about this for quite some time as we have seen more and more cases. Is there an advantage to earlier diagnosis? You could immediately then think about counseling the patient about transmission, et cetera, while we don't have the greatest data for this compared to HIV where many of the ongoing transmissions, a good proportion of them, are from other individuals who are acutely infected and not knowingly passing it on to their at-risk partners.

So, you can provide that earlier counseling and linkage to care earlier. There are a variety of treatment trials that are looking at treatment courses that are shorter than the typical courses given to patients with chronic hepatitis-C.

Is it a public health benefit for knowing where acute cases reside as opposed to chronic cases? That could talk about identifying patients and linking them early. And there's this concept of treatment as prevention, which is familiar to HIV and really many infectious diseases. Here we're talking about curing patients as a means of prevention by reducing the pool of patients able to transmit to others. Then one could think about, where you see more acute cases, devoting certain preventive and public health resources to that setting.

Now, there are some people who would say, well, you identify them early and a good percentage, 20, 30 percent, may just clear on their own and so there is no immediate clinical consequence. I still think there is a marker there to inform patients and talk about reinfection. Also, it's like, well, you're spending a lot of energy finding acute cases when you can really just find and cure them in the chronic phase. I just want to talk about acute a little bit more as it is relevant to this talk.

The antibody and molecular testing from a clinical standpoint sounds very simple, but there is actually potentially additional information that's available through these tests. There's the signal-to-cutoff ratio which rises over time, and related to that are

concepts regarding the antibody's avidity to the antigens and may be clinically relevant, as I will show you.

There's the potential for serotyping, which I would say has less clinical utility at this point, meaning serotyping and determining the genotype based on an antibody test. Whereas with molecular testing, there can be not only the quantification of the viremia but the identification of acute disease during that sero-negative window. In the end, the magnitude of viremia does not matter for treatment.

Genotype has been a standard third test which we are not necessarily discussing today although technically it is a nucleic acid test. Viral diversity is a factor that can be detected within detection of a quasi-species of virus such as hepatitis-C. One can also find embedded within the virus resistance testing information, so, resistance-associated substitutions within a given strain of virus that may be related to decreased activity of the agents that we're prescribing for these patients.

This is a slide from a study that looked at antibody avidity over time looking in various groups, including a sero-conversion panel, patients with chronic disease, and persons with resolved infection, and they do group differently as seen here. This is based on patients

since the last negative result. What you're seeing here is that perhaps early on you see these lower values of avidity. As patients have chronic infection, the antibody avidity rises and then after clearance decline over time. This is just one example of some information that could be available and may be relevant to earlier identification in patients.

This is a study that Barbara McGovern and we participated in from values of hepatitis-C RNA in patients who are in the acute phase versus the chronic phase. What you see here is significant overlap, but the typical chronic value is close to six logs; whereas, if you find a lower value that could be a marker for acute infection, again there is overlap. But, nonetheless, we consider this at least a potential marker that patients are in the acute phase when they might still clear the virus, et cetera.

Another piece of information is the viral diversity. Through the next-generation sequencing (NGS), one can infer transmitter and founder viruses. Moreover, you can quantify entropy scores from certain variants within the quasi-species within the nucleotide sequence. You can also look on a protein level. But these are just markers of Shannon entropy in the single nuclide variants which rise over time. Now, there is significant overlap in

these groups but I'm just stating that there is the potential to develop perhaps more specific markers.

In the state of Massachusetts where I reside, and where Al DeMaria who is on the phone presides over the infectious disease component of public health, there is an excellent system where all laboratory tests have real-time electronic reporting to the state, so, any positive test will be pinged there, and they are now trying to capture negative tests. Using an integrated surveillance system known as MAVEN they try to send the case report form to the clinician -- paper, not electronic -- and they occasionally get filled out. I do my best to fill them out and send them back.

Now, the age cut-off for patients is under 30, but because of this concern about young people who are acquiring hepatitis-C being a marker for acute disease and transmission, they have an enhanced case report form that tries to capture more information about those individuals who might be presenting with acute disease including the higher ALT and/or jaundice. And then onwards to CDC are these cases reported after applying the various definitions.

This system shows you the distribution of hepatitis-C as of 2002 in our state -- the so-called baby

boomer population which then was in their peak age around 45 and now is approaching 60 -- two-to-one male to female ratio, paralleled the data from national sources suggesting these infections, really millions of infections that occurred 30 years ago when we didn’t have safe blood supplies and universal precautions and some injection drug use from the 1980s, et cetera.

By 2009, this had turned into a bimodal distribution in our state, and if I showed you later graphs, actually, the group under 30 exceeds that of new cases identified within the baby boomer population. So this new wave of infections linked to injection drug use has been also detected in many other parts of the country. This sort of parallels either -- well, where they are counting cases is one thing. There are certain states that do not count cases very well. But you can see these greater than 50 percent increases both in New England where I am from, parts of Appalachia and other places.

Now, some of this may be enhanced case finding due to more resources to find, et cetera, but nonetheless, given the magnitude of the opioid epidemic, which everyone should be aware of in this country, a really huge public health crisis, this is one consequence -- new hepatitis-C cases.

This is a later graph from our state. Many of you may have noticed this on the previous graph, and I know there's perinatal expertise in the room. Now there are many places reporting increased evidence of, in this case, probably transmitted hepatitis-C antibody of young women of childbearing age, and even with an inefficient perinatal transmission rate often quoted around 6 percent, we are starting to see pings of babies being tested.

Then, a recent study led by the CDC has shown this increase in women of childbearing age; thus, this may be a particular target and many societies are considering expanded screening of, for instance, all pregnant women just as we do for all infectious diseases.

In the end, even with these great therapies, there is still a huge number of people who still need to be tested. We have had this concept of baby boomer testing for quite some time, and yet, we still have not achieved 100 percent coverage. There is a bottleneck there, just like the security screening that we encountered getting into the meeting today. You can have 99 percent effective therapies, but what good does it do you if you are not identifying cases?

The risk factor-based screening is a long list. When applying risk factor-based screening outside of the

baby boomer population, this is a long list of questions, many of which are stigmatized, and, from a clinical standpoint, you're asking these questions during the social history a few minutes after meeting a patient, and they may not trust you with everything that they have done in the past, even if they dabbled in this opioid injection stuff for a brief period in their lives. Moreover, young women, for instance, may have custody issues if they admit to such behaviors or have other reasons not to report that primary risk factor. Other things like asking about where tattoos were received, et cetera, these are all a little bit time-consuming to get at.

So, risk factor-based screening, I don't believe there has been a study that has shown that it has been applied effectively, and, thus, we are going to see more.

In the last few slides, this concept of two-step staging: initial visit, you do an antibody, maybe another visit to say if they are positive and talk about the next stage in testing. This is sort of where we were before in the previous era and is kind of cumbersome, and you are only partially a way through the workup for hepatitis-C.

Given that there is other information that we like such as genotype, et cetera, but now with pan-genotypic regimens -- I will still check it for the time

being, but there is the concept, well, do you need it if most genotypes will be treated with the same agent at least upfront, et cetera.

The magnitude of the viral load is a barrier that is overcome. The degree of fibrosis or cirrhosis, even prior treatment failure. Now we have new options. Resistance mutations actually. Because the therapies are so good, we often don't need to test for resistance mutations either at baseline or after treatment. It depends on what treatments you have available. HIV is no longer a barrier, and renal disease as well, with new agents.

This is a slide from the Foundation for Innovative New Diagnostics that shows you the previous workup, /again, two stages, perhaps three stages, with a genotype, biomarkers for the staging of cirrhosis. We no longer really use the next stage, IL28B, a genetic test. All those steps you can think about reducing, and we already have been reducing this to a primary workup that requires fewer steps. Perhaps in the future you will see fewer steps.

This is largely meant for impoverished settings, the developing world, perhaps something that the FDA doesn't need to consider today in their deliberations. But I will point out that if you go to places like West

Virginia with one of the highest rates of opioid overdose, if not the highest rate currently, as well as the associated hepatitis-C and other infectious complications, there are barriers to care for these high-risk individuals, the need for public transportation to healthcare facilities and labs, lack of insurance, lack of preventive services and mistrust of outsiders in hollows where a lot of the transmission may be taking place.

Now, with the more ideal world, in an initial visit you can do a point-of-care test for infection, gain all the information you might need, have reflex testing, for instance, have same visit results, have treatment applied perhaps by a pharmacist, maybe even over the phone, et cetera, and then test of cure. So, dramatic simplification and the same number of steps as before when we were just getting to the confirmation of infection may be the future.

It’s important to also note that we still need tools for reinfection screening, so, hepatitis-C RNA currently being used, and that patients after treatment, there can be relapse which occurs immediately after infection, and that’s when you’re testing for cure, and now is less than a couple percent of treated individuals. But then patients may have later relapse. That is very rare,

but if you find it later it’s more likely to be reinfection.

The take-home points -- The vast majority of hepatitis-C transmission and natural history is silent, thus requiring screening.

Testing may be useful for identifying recent transmissions and devoting public health resources.

Enhanced diagnosis would maximize the effectiveness of novel curative therapies. And screening is likely to expand to more populations such as pregnant women, their exposed children, pretty quickly, and perhaps more broadly to the U.S. population.

Less information is required to accomplish this treatment at this point, so that’s a factor in your deliberations. Things such as the magnitude of RNA, the genotype and resistance mutations are actually not necessary to accomplish most treatments.

The current testing algorithms may be improved to enhance or simplify clinical care. Thank you for your attention.

DR. CALIENDO: Thank you, Dr. Kim.

Our next speaker is Dr. Kamili from the Centers for Disease Control and Prevention. He is going to be talking about laboratory diagnosis of hepatitis.

Agenda Item: Laboratory Diagnosis of Hepatitis

DR. KAMILI: Good morning. Thank you very much for the invitation to present here. In my talk, I will focus on the laboratory diagnostics of hepatitis-C.

As background, if you look at the overall diagnostic landscape of viral hepatitis, we all know the viral hepatitis is A through E because of illness, the signs and symptoms of which are clinically indistinguishable; therefore, we have to employ testing of the various serologic markers that are listed on this slide to establish the etiology of infection.

If you compare the two blood-borne pathogens here, HBV and HCV, whereas HBV provides a rich area of markers for diagnosis for stages of infection, the field of HCV is limited to just three markers, and only two of them, the antibody and RNA, are available in the United States.

It was already described by Dr. Kim, so what I want to highlight here is acute HCV infection or chronic HCV infection, and these markers are presented in both stages. There is no marker for the diagnosis of acute HCV infection. Some of the research methodologies that can help and have the potential of differentiating acute from chronic were just discussed by Dr. Kim.

So, what is the order of appearance of these markers? We know after exposure, HCV RNA is detectable within the first two weeks after exposure. At CDC, a decade back when we were conducting studies in the chimpanzee model, experimental infectivity studies, we found that you could detect HCV RNA within three days after they were inoculated with very high titers.

HCV core antigen, which is not available in the United States, is concordant with the appearance of HCV RNA. If you look at soft antibodies, which is -- I referred to this as anti-HCV but we all know this is IgG anti-HCV, and these become available after about 11 weeks after exposure resulting in this long window phase of about 11 weeks when the only marker that is detectable is HCV RNA. I will talk in a little more detail about each of these markers. Some of these have already been discussed in the previous talk.

Anti-HCV indicates exposure to HCV and this antibody is present in all the states of infection -- acute, resolved as a less chronic phase of infection. There are FDA-approved assays, both enzyme immunoassays and chemiluminescence assays, and we also have now an FDA-approved rapid test for anti-HCV. Previously, we used to have a supplemental confirmatory assay, RIBA, recombinant

immunoblot. It is no longer available now in the United States. It was used to confirm the screening reactivity.

A little bit about the antigenic composition of these various diagnostic assays. As you know, the first anti-HCV assay that was available more than a decade back had just one antigenic fragment, and over the subsequent generations more antigenic components were added to these assays resulting in enhanced sensitivity and specificity of these assays. As you will see in this slide, whereas the first generation of anti-HCV assay was detecting antibodies, after about 21 weeks after exposure, with the addition of these antigenic components with improvement in the diagnostic assays, the third generation assay now has cut this down by one-third, so we are to detect antibodies by about 11 weeks instead of 21 weeks in the first-generation assay.

Listed on this slide are the assays that have been approved by FDA for screening. In 2003, CDC published the first testing guidelines. I just want to highlight here one of the aspects that was mentioned also earlier, which is the signal-to-cutoff ratio. Any diagnostic assay we know has a potential of false positives, especially when you are testing low-risk populations.

At that time, every screening test was confirmed by RIBA, so CDC at that time tested about 25,000 samples from different populations from low-risk to high-risk and came up with these signal-to-cutoff ratios that are shown here on the right hand side in the table. We found, for example, that for one of the assays, if the signal-to-cutoff ratio was less 3.8, only about 4 percent of those could be confirmed by RIBA. If the signal-to-cutoff ratio was greater than 3.8, you could confirm all of them. so RIBA did not need to be performed on these assays.

These are old guidelines and the only reason I am showing them here now is that we know that some of the clinical labs still incorrectly use signal-to-cutoff ratios. These are very specific for each of the assays. We have heard that some labs will use 3.8, although they are using an assay where the signal-to-cutoff ratio threshold is lower. That’s the only reason I brought up this slide.

Since then, over the course of the last 10 years with all the developments in the field of hepatitis-C, we have rapid tests now. It’s not quantitative, there is no signal-to-cutoff ratio associated with it. RIBA has been discontinued, and we all know now that we have highly efficacious antiviral therapies that achieve cure in almost all treated patients.

We updated our guidelines in 2013 and focused on the identification of current infection. If you look at the left hand side, you test a person for antibody. If negative that means the person is not exposed. If the antibody is positive, you directly test for HCV RNA, not worrying about confirmation of the antibody tested so that you can identify individuals who are currently infected that could be referred to curative treatment.

Some of the considerations that need to be taken into account are listed here in this slide that shows the interpretation of these results. If both tests are negative it indicates no infection. If both tests are positive, that could indicate either acute or chronic infection. This third category is if antibody is negative and HCV RNA is positive, and that could indicate a window phase infection like in the case of needle stick injuries. It could indicate delayed seroconversion like we find in the immune-compromised individuals.

Finally, if antibody is positive and HCV RNA is negative, that could indicate any of these scenarios here, which include a resolved infection, or it could indicate a cure and the individual was receiving therapy and is now RNA-negative. And, of course, there’s the potential of false anti-HCV positivity, and there are some studies that

have also shown there may be a few cases of intermittent viremia.

This table shows the HCV RNA detection methodologies that have been approved and they have excellent performance characteristics. Look at this last column with the limit of detection -- as low as 5 international units to 50 international units. They have excellent performance characteristics and they are pan-genotypic.

Since our publication of these revised testing guidelines, we have heard about the challenges in the implementation of these testing guidelines. Some of these are, of course, the cost -- all the clinical labs do not perform HCV RNA testing. We know IBLHL did a survey sometime back about the number of labs that are doing the testing for HCV RNA and found only 33 percent of the labs were doing HCV RNA testing.

One of the challenges that Dr. Kim mentioned earlier is can we use the same sample that’s tested for antibody and use the same sample for HCV RNA without worrying about contamination. We all know HCV RNA methodologies are ultra-sensitive and even the slightest level of contamination can generate false positives, so we have just done these studies at CDC to look at can you use

the same tube that you used for the antibody test for HCV RNA test.

We looked at these four platforms -- the Ortho platform, the Centaur platform, Elecsys and ARCHITECT platforms. All these serologic platforms are automated and there are different types of settings shown here. You can either have circular racks or you can have horizontal racks. What we did was we interspersed samples that were HCV RNA-negative with HCV RNA-positive samples with various HCV RNA titers. The colored darts indicate these were high-titer HCV RNA positives, and the hollow ones were HCV RNA negative.

We tested them with the Roche HCV-RNA test and we found that those platforms that use a fixed probe -- one platform that used a fixed probe had a low level of contamination. All the other platforms that used a disposable tip for sample transfer did not have any evidence of contamination. So we know there is only one platform at this time that used a fixed metallic probe. Once it takes a sample it goes through a washing step and then takes the second sample, so it was only that platform that we found had a low level of contamination at the lowest limit of quantitation.

Based on this study, it is feasible to use the same sample for both antibody and HCV RNA without having to call the patient back for a second blood draw. And then sometimes you lose the patients to follow-up.

I want to talk a little bit about the only point-of-care test for HCV RNA. We all know it is not approved by FDA yet. This is the Xpert system by SAFER. I have listed here two studies that have shown an excellent concordance of this point-of-care test with the Abbott HCV RNA test.

On the left hand side are more than 200 samples that had similar HCR RNA titers whether they were tested by the Xpert system or the Abbott system. On the right hand side, the blue bars indicate the HCV RNA titers by Abbott and the red bars by the Xpert system. As you can see, these patients were followed from baseline to 24 weeks and there was almost perfect concordance in the HCV RNA titers.

Just last week this paper was available online. They have now published the feasibility of this methodology using finger sticks. They found all the samples that were detectable by the Abbott test were also detectable by this system when the finger stick was used.

The HCV core antigen test is not available yet in the United States. Here, we have two studies listed that have again shown an excellent concordance with HCV RNA

levels. We know one of the limitations of the core antigen test is that it is not detectable when the HCV RNA levels are below 2,000 international units. The significant advantages of this test are that you require a smaller sample volume; you don't need a pristine sample for core antigen testing.

On the left side it shows the profile of a patient that was treated at that time with interferon. You can see the HCV RNA levels, and the red column shows the HCV core antigen levels perfectly concordant with the HCV RNA.

At CDC we did an independent evaluation of this core antigen test based on testing of an evaluation panel of about 500 samples. We had about 70 samples from the window phase of infection. They were all antibody-negative HCV RNA-positive, and you can see here that we detected HCV core antigen in all of those cases. In the post-seroconversion phase, the sensitivity of core antigen was about 94 percent.

Once we are able to identify a person who is currently infected, HCV-RNA-positive, the sequencing technologies offer us tremendous opportunities to look at all these different aspects. One can determine the genotype. We have been using sequencing for outbreak

investigations to establish any transmission links and recombinants and other phylodynamic studies, so, we are moving now into next-generation sequencing technology. Traditionally, we have used Sanger sequencing. I will show you the power of this technology in a moment.

HCV, as we know, is an RNA virus. There is a tremendous variability across the genome of this virus, as you can see here. Because of this variability, different regions of the genome are used for different purposes. The 5’ UTR is used for diagnostic purposes because it is fairly conserved across all genotypes.

I would like to draw your attention toward the HVR1 region here. HVR1, which is located within the E1-E2 region, is the most variable region of the HCV genome. We have been employing and exploiting this variability to establish transmission links. We have been using this region for sequencing in outbreak transmission studies and in organ donor-related transmission studies.

As you can see here, these are four patients. All four patients have HCV genotype 1E infection. If you were to look at sequences based on 5’ UTR or ns5b they would be on the same plane. But if we look at HVR1 sequences, all these sequences cluster together based on the patient.

Every patient has a unique signature pattern of HVR1 sequences.

In this one you can see on the left hand side, we have been using this approach to establish any transmission links. What you see here in the blue shaded circle is the sequences from a surgical technician -- this has been published in 2015 -- the sequences of a surgical technician and five patients who were infected at that clinic. The sequences of those patients and the sequences from the surgical technician, shown by the green bubbles, intermingle together. Whereas, the sequences from the control patients -- which you see here; some of them are from NHANES participants -- were distinct. None of them showed any relation to the sequences from this surgical technician, who has since then been implicated in this transmission study -- were clearly mingling with the patients that he came across with.

We are taking it to the next level. At CDC we have developed this technology which we call GHOST, or Global Hepatitis Outbreak Surveillance Technology. This system is based on a combination of bioinformatics tools and computation methodologies and uses next-generation sequencing. It is available online. Any lab, any investigator who has the capacity of generating sequences

using the NGS can upload their sequences on the system online and then can see if there are any transmission linkages.

What you see here is the output that you get once you have uploaded the sequences. Each of the nodes represents sequences from a patient, and if there are any linkages there that means there is evidence of transmission among those participants. We have successfully used this system recently, a few years back, in the Scott County, Indiana HIV HCV outbreak. As you can see, we identified a number of clusters of HCV transmission among the users in the county.

What we plan to do in the next few years is we will have a smartphone version of this system. If you are an epidemiologist and are in the field and if your lab has submitted sequences and you want to find out whether there are any transmission patterns, you can actually access the results from your smartphone. So we are really excited about the system.

ABHL folks are here; they have been tremendously helpful to us in the implementation and the training of the state labs. So far, we have trained 22 state health labs in this technology. We did a pilot project with five of the states and three state health labs are independently

implementing and have successfully used the system for their outbreak investigations.

To summarize, we see that the antibody test for hepatitis-C is only useful to determine exposure to HCV; it does not differentiate between acute, chronic and resolved phase of infection.

HCV RNA and core antigen, which is not available here, remain the only marker if you want to identify and diagnose active infection. Next-generation sequencing technologies do provide tremendous opportunities for outbreak investigations, transmission studies and other phylodynamic studies.

Since we are embarking on various elimination programs for hepatitis-B and C, I think what I call the three As of diagnostics -- accurate, affordable and accessible -- are the keys to any elimination program.

And I want to conclude with this slide, which was presented at last year’s American Association for the Study of Liver Disease meeting. These authors presented this data that if the diagnostics in HCV are not made readily available and accessible, we may reach a stage which they call diagnostic burnout. They looked at the data from three countries, Brazil, Spain and Portugal, with varying disease burdens, and they looked at the 2016 data.

They found that, by 2016, the rates of detection of HCV infections had dropped to less than 2 percent, and they estimate that unless we really improve diagnostics and unless we really make the diagnostics accessible readily and at a cheaper rate, within the next four years these three countries may reach a stage where they will have no identified cases of HCV.

If you look at the disease burden, there are 1.8 million cases in Brazil. There are two therapies available now. The costs are getting lower, but they may not be individuals that are identified that could be for cure and treatment. I think that is consistent with the theme of this meeting, that we need to identify these individuals who are infected so there could be an effort for cure and treatment.

With this, I want to thank you for your attention.

Agenda Item: Questions for the Speakers

DR. CALIENDO: Thank you. We are going to open this up to the first three speakers for questions from the panel. Please introduce yourself if you have a question so that people who are taking notes and keeping track of everything can do that a little easier.

I have a question on diagnostics. You talked about viral diversity. Can you give us a perspective on how much you think that impacts the performance of the serology and RNA testing? I bring it up thinking in the context of special controls. Is this something that we should worry about? We worry about it a lot with HIV, but is it the same issue with hepatitis-C with these diagnostic tests?

DR. KAMILI: The short answer is no. We have tested a number of pan-genotypic panels not only from the United States but from different parts of the world, and we have not seen any evidence so far that if you have different genotypes that they have any impact on either the detection of HCV RNA or on detection of the antibodies.

We also see the same for the core antigen where we did include samples from genotypes. So far, the viral diversity does not have any impact on the detection by either RNA or by antibodies.

DR. MILLER: I just want to clarify your response to that. You said per genotype. Was this based on whole genome sequencing or ns5b genotype -- for diversity?

DR. KAMILI: The diversity here -- We’re looking at the viral diversity from the angle of the HVR1 region, but as a standard algorithm that we use, we determine the genotype using ns5b because that cuts down on the number of

sequences that you have to analyze. Once you have done the preliminary genotyping using ns5b, then we use the HVR1 region which provides the information about genotype as well as all the other clustering of sequencing and transmission studies that you can use it for.

So, again, based on I would say thousands of samples, we have not yet seen a case where you could get a different genotype if you use ns5b or if you use any other region.

DR. MILLER: Did you see any under-quantification based upon that diversity? In the chart you showed, in the 5-prime UTR region, it was always less than 10 percent. I forget what was on your axis, some sort of diversity I believe. Within that 10 percent diversity, you did not see under-quantification of viral load assays?

DR. KAMILI: That is an excellent point. Sometimes, what you see is that if you have a low-titer sample, you are not able to amplify all the regions. If you have, for example, viral titers in the range of five logs and six logs, regardless of the region you want to amplify, you can amplify it. But if you have a low-titer sample, let’s say three logs, we have seen challenges sometimes in HVR1 amplification. So, unless we enrich the sample or we

use more of the template, we can amplify enough HVR1 sequences.

But we have not seen an association of the viral titer with the detection if you use ns5b or 5' UTR regions.

DR. WARD: Saleem, you brought up core antigen and its place in providing perhaps a more readily accessible and more affordable way of diagnosing current hepatitis-C infection, but it is different than PCR. I have a question for the committee just so I can understand whether that would be considered a *de novo* product or would it be an extension of the current methodology. Would it be a Class III or could it be a Class II, as an example of a new technology?

DR. GITTERMAN: That is a very good question. I think it would be fair to say, right now, again, as the HCVI committee are concerned, it would be considered Class III. Even though I cannot commit to it -- I cannot individually do that -- one could reasonably infer that if the committee does vote for reclassification of the existing devices, that in fact, exactly as you suggested, it would likely come in as a *de novo* at that point. Is that clear?

DR. WARD: Yes, it's clear. It is unfortunate. I think one of the aims of this change is to make it less

burdensome for innovation and innovative products to come out and help us resolve this problem of a lot of people not knowing their status.

I also heard you say sort of it depends sometimes.

DR. GITTERMAN: Absolutely. I am speaking very generally. Certainly one could make a case that, even as it exists now, HCV, perhaps it would be less risky. But if I were just to make a gross generalization, if there were reclassification -- depending on the discussion. I mean, it is not an either/or. The points people make in the discussion will be very interesting. But one would very likely say that if the existing devices are reclassified it would not be an issue of having HCV antigen coming in as a *de novo*.

Again, though, we are not asking you necessarily to reclassify everything. The discussion will be very interesting on what people think.

DR. WARD: I have a follow-up because I was trying to understand the materials. Arthur, you brought up the algorithm for testing, as did Saleem, but there may be some populations where the antibody as the first-order test would actually be not necessary, such as testing people who had been cured before but then have an ongoing risk

behavior and, also perhaps, even for young children where PCR testing early in life is preferable to waiting and having to delay testing for the antibody to appear. But yet, when I was reading the FDA materials, it looked like the labeling, if you will, for the use of PCR is to be after the antibody test is done.

So I am very interested to see if that is, indeed, the case because I think we really need first line viremic testing rather than always to be followed by antibody testing. But if we go that way, again, does that require a Class III labeling or can that be something that this committee could help bring about to a Class II?

DR. GITTERMAN: I have to say these are excellent questions. I would also say we are very reasonable people, and there is no need to be burdensome. The fact is we can look at things. There are qualitative RNA tests as you are aware, but these are all very interesting points which is why we have gotten together this august body.

But you obviously read the materials.

DR. KIM: Dr. Ward, I would agree that from a clinical standpoint what we're interested in is treating the viremia. So, a yes/no question, basically. So, skipping the antibody portion -- although I tried to describe some other applications for that antibody including markers of

exposure, et cetera, that can be useful -- I concur that skipping directly to viremia would be important.

DR. WARD: In some situations, not all situations.

DR. KIM: Not all, of course.

DR. SCHERF: Just to add to Dr. Gitterman's point, I think if we're able to identify the risks and then, as you said, you then use a certain algorithm and want to have a certain kind of strategy, I think if the risk can be addressed, then there will not be the need to either have any of the other analyzing that may be coming into play being a Class III. So I think it's really driven by the associated risks and the opportunities to move it into this other class that we are proposing.

DR. CALIENDO: Can I interpret that to mean that we are here today to talk about the tests, not the algorithms and how they would be used? If the committee decides that they are comfortable with Class II, then how they are put together clinically is a completely separate issue and really not on the table. Is that a correct assessment?

DR. GITTERMAN: That is absolutely correct. I would also ask, too, that since HCV antigen is not on the table right now -- I think Dr. Ward's points are excellent -- but I would urge the committee not to really discuss HCV

antigen *per se*. Although, if there is anybody watching or in the audience from a company that is developing such a test, we would welcome it in many ways and would love to be involved in that discussion.

DR. THOMAS: Arthur, could you say something about what's known about the duration of time in average clinical practice between the screening test becoming positive and the confirmatory test being done, and how often that does not occur?

DR. KIM: Sure. It's clear that assays such as the reflex test basically allow quick confirmation of positive antibodies, but that is not always available outside of Quest and other settings. In a hospital setting such as ours which does testing, there could be substantial delay in re-drawing patients for that second test. I would say that could last weeks to months. And if you think about settings such as jails and prisons where there's screening going on, I would hazard to say that it can take really quite a long time.

There are so many drop-offs in every step of the care cascade, so to speak, that really, even just the first diagnosis -- you saw that big drop-off. That's where you get a lot of drop-off in terms of the confirmation of viremia, and then even the linkage afterward so people can

be told they have it, and it still take even years to reach that point. So, anything that accelerates that process I would say is a clinical boon. If you could tell them the same day accurately and affordably and that would meet those criteria, that would be a total boon to places where we are trying to accomplish high throughput testing.

DR. CALIENDO: We are going to go to the phone. Our patient rep is on the phone. Could you please introduce yourself, and then I understand you have a comment or question. After that it's Judy, David and Melissa.

MS. LUPOLE: This is Patricia Lupole. I am the patient representative and I have a question.

Dr. Kim, basically, if I understand correctly, with antibody testing you feel that the need for genotyping and finding resistance genes would not necessarily be needed. We have found a percentage where by not knowing their genotype their odds of clearing the virus are diminished. Could you speak a little more about that?

DR. KIM: Sure. At this point in the stage of drug development, if I understand your question I think you are stating that genotype did modulate the treatment response. With today's therapies, the first line therapies that are available, what we would call pan-genotypic therapies, there's little difference between genotypes. I would not

say there's zero difference, but there's not enough clinical difference to say that a 97 percent response rate for genotype 3, for instance, for one of the agents, is that different than a 99 percent for genotype 1 using the same agent. So, if somebody has never been treated before, one could argue that ultimately the genotype does not change management.

I would, however, emphasize in a sort of mixed-message sort of way that understanding that genotype can be useful for distinguishing later -- I glossed over this at the end, but -- for reinfection purposes. If a patient switches genotypes, one does not need the fancy phylogenetics to distinguish a new 1A virus from the old 1A virus. If you have a new genotype you are clearly re-infected.

MS. LUPOLE: Agreed.

DR. KIM: So that kind of explains what I was trying to convey regarding the genotype test -- that ultimately, clinically, you don't need it quite so much for the treatment but that there are still uses for it.

MS. LUPOLE: Yes. There is a pronounced difference in pricing. This knowledge that you're explaining to us, making this available to the medical community, would that also be an option where a person, say, with genotype 3

isn’t placed on a product with even lower odds of clearing, as low as 86 percent in some of the studies I have read. Can you comment on that?

DR. KIM: Yes. I’m sorry for not including the slides based on genotype. The treatment response rates that you’re quoting, the 86 percent for instance for genotype 3 for first line therapies, I have to say with the most recently approved -- which is literally in the last year, 2017 -- we’re talking about naïve patients receiving some of these agents, and the difference is now closer to 99 percent for genotype 1 versus 97 percent for genotype 3 in patients who have never been treated before.

So, while I would agree that that difference was very important as recently as just a year ago, we are reaching the point where one could at least argue that initial genotype for most patients is not 100 percent necessary. I would still get it as of today until this is proven, and, as mentioned, there is still public health and other tracking information embedded in the genotype and in molecular information.

We are just talking about the novel therapies as of last year narrowing that gap, if I understand your question correctly.

MS. LUPOLE: Yes. I think cost is a big factor, especially with insurance companies, and that information would be vital right now. But I see where this is headed and I understand what you're saying. Are we there yet, I guess would be the question. But thank you, sir.

DR. BAKER: Judith Baker. My question is concerning the women of childbearing age. I am wondering if women in that population, if they were adequately represented in the samples that Dr. Kamili was describing.

DR. KAMILI: I really don't know how to answer that question, what would be the adequate number of the samples included, but I know that there were not as many samples from pregnant women as we had from, for example, the blood donors, the IDU population. I do not remember off the top of my head what was the actual number.

Currently, as we speak, we are looking at a perinatal workgroup that's looking at the transmission of HCV from pregnant women to their children. We are looking at the proportion of women that test HCV-positive and how many of them are HCV RNA-positive, too, and what is the rate of false positivity, what is the concordance between different assays. That is a significant sample set there that can be used to address this question.

DR. BAKER: Thank you.

DR. KIMBERLIN: Can you comment on the performance characteristics of the RNA PCR assays in neonates and very young infants? I believe at the current time the American Academy of Pediatrics and, to my knowledge, CDC as well recommend antibody testing out at 18 months and beyond to rule out hepatitis-C and allow for testing as early as one or two months of age with RNA PCR but does not lead with that.

What do we know about either of those diagnostic assays in very young babies? I am talking about in the matter of weeks or just the first few months of life.

DR. KAMILI: The short answer is that we know very little because of the lack of availability of the samples. I have one slide I did not show where we are looking at the feasibility of using dried blood spots. That is what you have available from the neonates at birth, the heel sticks, to see whether we can effectively detect HCV RNA from blood spots.

We already published one study where we found that you can detect HCV RNA concordantly from dried blood spots and serum or plasma samples, although there is a drop in the sensitivity because, as you all know, the amount of sample that you have with a DBS is significantly less than when you use the serum or plasma samples.

Dr. Ward, who is here from CDC, I think established a workgroup to address this issue to see whether we can revise or have separate guidelines for neonatal testing. The first step would be actually to start looking at the feasibility of testing the heel stick samples for HCV RNA and really test them. Until then, I think the current recommendations remain.

DR. KIM: I would point out that given the epidemiology of hepatitis-C you have baby boomers who gave birth in the 1980s before we had identification of this agent, so, really, now represents the time when there is opportunity to answer your question. We did not have that opportunity 30 years ago. Because of this new wave of childbearing women or women of reproductive potential we have a new opportunity to understand the questions of how much is in core blood, how much is in heel sticks, et cetera.

DR. KIMBERLIN: With that lack of understanding of the performance, does that have an impact on our considerations at least as it applies to babies and very young infants in moving these from a Class III to a Class II?

DR. GITTERMAN: it depends. I will answer two ways. One is, in the intended use for a device, labeling

will clearly state what is known, but if no information is known it will reflect that.

But, as a second answer, given the discussion, FDA of course strives to be as inclusive as possible. This calls for, if there were some type of bank or some type of resource that companies in this space could go to, a pre-arranged panel that was not necessarily selected for, that would go a tremendous way rather than asking every sponsor to go out and get these types of samples.

So the question is we would describe what is known, and one is we would hope very much, given the importance of this population, that it would be addressed. And two, there are things that the government and private industry can do to make this far more accessible for industry by doing it. We should not expect for a very special vulnerable population that every company is going to have the resources to go out and do a study where the prevalence, as you saw, is fairly low. So the answer is this would not be preventative.

And again, in your case, one could argue does that PMA versus the 510K make that bit a difference? No. It would still describe what is known. But we can certainly put the committee on record, based on your one comment, as perhaps saying that this is a very important population and

you emphasize that FDA should go to efforts to make sure this is included in products that come forward.

Is that a fair way of summarizing it?

R. KIMBERLIN: Sounds good to me.

DR. MILLER: I have two questions. Again, I want to go back to the diversity because it's very important for me to understand the risks associated with this in thinking about reclassification

Dr. Kim, could you please comment? You had a slide about the Shannon entropy related to a per-patient diversity increase over the time of chronic infection. What do we know about the risk of this associated -- again, this would be mostly for nucleic acid tests -- in under-quantifying or a false negative result based upon this increase in entropy and entropy over time? And do we know the risk enough to even comment on that?

DR. KIM: That's a good question. I don't do those types of studies but I provide samples to labs that do try to do that sort of work as well as to the phylodynamic and linkage of cases. I would say the risks of all that testing could be classified as the following.

In terms of sensitivity, I think if you have a value you could probably, with these ultra-sensitive assays, have detected the RNA, so the risk of false

negative at least for detection of viremia seems to be low, if I understand your question.

The risk of misclassification of patients into acute versus chronic could be there in the sense that, as I showed you, there is overlap between the groups, a little bit less than perhaps the avidity cutoffs that I was showing for the antibody test. So perhaps there is risk, if we were using that for that purpose, of misclassification.

Now, whether that risk is to the patient or more to the public health, not devoting resources to the right place or devoting them to the wrong place, is a broader question.

DR. MILLER: That is helpful.

DR. KAMILI: So, I want to add to this one. We have followed patients through from about eight to 12 years, and we looked at the Shannon entropy and we looked at the divergence of the species. In several patients -- I don’t have the slide -- if you could show the phylogenetic tree it would look as if there are two different viruses completely evolved into a different species. Same genotype. But throughout the course of the infection -- because we had sequential samples -- at no stage in the follow-up was HCV RNA undetectable.

So it remained detectable throughout even though, if you look at the baseline sample versus the sample collected at 12 years after follow-up, the sequence diversity was huge like they were two separate plates; yet HCV RNA remained detectable.

DR. CALIENDO: Just to comment, the entropy is for ns5b, which is not where we are targeting. I think that's kind of what was addressed initially. In the area where these tests target, we don't have that same data. Is that correct? We don't see that same diversity?

DR. KAMILI: The diversity is lesser in those regions compared to the HVR1, where I showed the variability plot. But in terms of the detection by the assays where the primers were always designed in the regions, where there's minimal diversity, there is never a relationship of the diversity with the lack of detection by any of the assays.

DR. MILLER: So that is a qualitative result. What about the quantitative results? There have been recalls of assays due to the under-quantification of specific genotypes. Did you see that at all?

DR. KAMILI: Since we are not a clinical lab, we switched to the quantitative assay a long time back because earlier you had to use the two-step approach where you

would first use qualitative, quantitative which had 600 international units limit of detection. If negative, then you would go for qual, which was more sensitive.

So I would say for the last 9, 10 years we have switched to quantitative assays; we don't use qualitative assays anymore. And the data I am presenting here is all based on the quantitative assays, which have the similar level of detection as the qualitative assays.

DR. MILLER: I think you are still commenting on what the qualitative result was. There was no negative. But did you see any variability in the ability to quantify?

DR. KAMILI: No.

DR. MILLER: Okay. My other comment was related to the reflex testing data that you presented from the CDC, which was very nice. Thank you for sharing that.

For labs that have taken this on, keep in mind that specimens coming through the lab for antibody testing are largely processed in chemistry core laboratories that go through automated systems and may be aliquoted into additional tubes, so it's important to also consider the potential risk of contamination that occurs before it even gets to the immunology or molecular laboratory.

DR. DODD: Lorie Dodd. I have two questions. The first question is for the FDA and we can consider posing

this question later in the day but I will ask now. I was just curious, are there any lessons to be learned from the reclassification of the CMV and EBV testing that was mentioned in the earlier talks? I just want to put that out there and I will move to the second question.

This question relates to the reclassification and what kinds of predicate devices one can compare the new tests to. One concern that a statistician might have is biodrift. If you're comparing it to a predicate device that may have a slightly lower sensitivity and specificity and you approve it based on that, and then you have another test, that test has now lower sensitivity and specificity.

I just want to bring that up and actually want to ask you, as well as the other two speakers behind me, if there are any special controls that could be considered or should be considered to avoid that kind of drift in diagnostic accuracy.

DR. GITTERMAN: I can answer three questions at once. One is the slippery slope is a major concern, and Dr. Garcia will describe that exactly.

What have we learned from CMV? We learned it's pretty tough. I think what will be reflected in Dr. Schlottmann's talk is a lot of what we have learned about CMV in the proposal.

But I could answer Dr. Miller's question, and that goes back to the unknown unknowns. Obviously, most manufacturers will try and pick very, very conserved regions; yet, it sometimes does not work. As you are certainly aware from CMV, in that case they picked regions that should never ever fail to pick off primers, but they did.

Now, this is not flu. Flu, as you're probably aware, does have a panel because of the known mutations. That in fact is checked every year and that has been a major issue. When they pick these regions the assumption is they will be good forever. Now, we know that doesn't happen, and how one could address that in special controls Dr. Caliendo will address. Whether that, in fact, would be different between a PMA and a 510K is unknown. But to date, all the devices look good. If we didn't do that, there would be a recall in that case.

But it's very difficult, and if it does appear it's going to be in a very small percentage. In that case, you are going to have to have some comparator, so somebody is going to have to realize and have enough insight and have another test that uses different primers that in fact picks it up.

So I would reserve this, if there is discussion of this, to the committee later because it is a concern with any viral disease, what to do about mutation. But also, as either Dr. Garcia or Dr. Schlottmann will mention, the requirements in terms of looking at diversity, looking at the samples that are chosen, are encompassing the fact that we don't want to miss it right off the bat. That is a given.

But it is a very good question. The hope is that the viruses don't get that much smarter but our diagnostic tests do. But there is no way to prevent it by hopefully just being as conservative as possible.

DR. LEWIS: My question is actually a generalization of Dr. Dodd's question, and that has to do with the FDA's experience over time with the reclassification process. I would be curious if there are any examples from the broader experience of reclassification from Class III to Class II that would represent cautionary tales either as perceived from within the FDA or from the larger laboratory community.

DR. GITTERMAN: I would defer -- I do not know of one. Now, never say never. But I would defer to -- there are a number of FDA personnel within the room.

I would just say for our division, we don't have that many Class III devices so it is not easy for us to say within the microbiology devices community that there is a broad experience. But I can't say that this has been a tremendous red flag previously.

However, I think the reason for that is the special controls have been very, very carefully written, often with the expertise of the committee. We have previously brought two products to the committee -- three actually -- TB products, detection of TB, not latent TB -- that were reclassified. We brought CMV to EBV which were in process, although I will make the point that EBV has not been cleared so that would be a *de novo* product, which was discussed at the committee. And this is the third meeting we have had.

I don't think there is a broad experience I could touch on but I do think it really is because we have listened very carefully, and the special controls I think have been very, very thoroughly and carefully thought about. We will probably hear some more from Mr. Spring about that, too.

But that is why the committee is here, to hear the recommendations, if there is a consensus that reclassification is acceptable, for what you see could

result in that. Dr. Schlottmann will talk about that a little bit. We don't want to get into a discussion of every special control, but, as a generalization, from what you have seen and the background, could this result in safe and effective devices.

DR. SCHERF: I think we are also in a unique position now after some of these PMAs have been used for a good number of years -- and Dr. Schlottmann will go into the timetable there -- we actually have now the body of evidence that helps us to kind of think about the risks and maybe also define some of the special controls that we believe are usable to really then have an opportunity to down-classify that. I think that was not the case before. First of all, we don't have too many PMAs in our division, but really the body of evidence is now so expanded that we feel comfortable considering this type of move.

DR. LEWIS: Just to clarify the philosophy of my question, I am actually trying to get you away from thinking about what you think you know about hepatitis-C. I am asking about broad experience with the process.

What I actually heard from your answer is that there's an N of 3 and you haven't gotten into trouble yet.

DR. GITTERMAN: Well, the process we think is fine. The result we can't say --

DR. LEWIS: I just want the data, and the data is N is 3, and so far we are good.

DR. GITTERMAN: But can I make a qualification? That doesn't mean the PMA process is perfect, either. You can get into problems both ways, and you do introduce some concerns. But as you will hear later, there are some additional mitigations in the PMA process.

DR. LEWIS: So if the control group is the PMA process, there were three; we moved them into the test group and we are still good with three for three.

DR. GITTERMAN: That would be a fine way of describing it.

DR. CALIENDO: We are going to move on because we have quite a bit of time this afternoon to continue. This is an excellent discussion, but I want to have a chance to get you guys to lunch before it gets too late.

We are going to move to Dr. Garcia's talk. Dr. Garcia is from CDHR. She is going to be talking about the FDA perspective on risk/benefit of HCV serology and molecular assay reclassification.

Agenda Item: FDA Perspective on Benefit/Risk of HCV Serology and Molecular Assay Reclassification

DR. GARCIA: Welcome. I am Dr. Ines Garcia, a reviewer in the Division of Microbiology Devices. It is

difficult to follow the previous excellent presentations by Drs. Kim and Kamili, but I will try to give you an overview of the FDA's perspective on the reclassification of HCV serology and molecular devices.

Knowledge mitigates risk. This slide shows a general schematic of how FDA analyzes knowledge and risk of an analyte or device to determine the proper classification -- Class I, Class II or Class III. Devices or analytes for which there is the lowest risk to a patient and for which we have the most knowledge are placed into Class I. Devices or analytes for which there is the highest risk to a patient and for which we have the least knowledge are placed into Class III.

It is possible, as our knowledge of a device or analyte increases, that we are able to mitigate the risks of the device through special controls allowing it to be placed in a lower class. As you can see here, special controls once again become a key piece of the discussion. As device class increases from Class I to Class II to Class III the regulatory controls also increase, with Class I devices or analytes subject to the least regulatory control and Class III devices subject to the most stringent regulatory controls.

For Class I devices or analytes, general controls, as you have already heard before, include prohibition against adulteration and misbranding. Manufacturers are simply required to list their establishment and the devices they market. Manufacturing must be done according to quality system regulations and GMPs, and adverse events are reported.

For Class II devices or analytes these controls apply, and special controls are specifically tailored to each device. These will be discussed in this talk and the next.

For Class III devices or analytes, these general controls apply and a PMA is necessary for marketing of the device. All of the devices being discussed today are Class III and are being considered for down-classification to Class II.

When is a device a Class III? It is purported or represented to be for a use in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury. It is also a device that cannot be classified into Class II because risks cannot be mitigated through special controls

to provide reasonable assurance of safety and effectiveness.

What is necessary for the approval of a PMA Class III device? There must be valid scientific evidence that the probable benefits to health from the use of the device when accompanied by adequate directions and warnings outweigh any probable risks. Similarly, based on valid scientific evidence there is reasonable assurance that a device is effective under the same conditions as just stated.

Since we are considering reclassification for Class III devices into Class II with special controls, what are Class II devices? They cannot be classified into Class I because the general controls are insufficient to provide reasonable assurance of safety and effectiveness of such devices, and there is sufficient information to establish special controls to provide such assurance. Class II devices typically require premarket notification and clearance to FDA, such as with a 510K, prior to being marketed.

What does FDA usually require for a PMA and a 510K application? These are the data needs for both premarket applications, PMAs, and premarket notifications, 510Ks: precision, accuracy, reactivity, sensitivity,

specificity, both interference and cross-reactivity, metrics studies, sample preparation if relevant, linearity, performance around the limits of quantitation or the cutoffs, carry-over and assay stability. As you can see, the analytical studies will not change with reclassification.

As we have already heard, there are differences between Class III and Class II device submissions. PMAs, Class III, contain a manufacturing section in the submission. Similar studies are conducted for the 510K but they are not required to be submitted; however, manufacturing information must be maintained at the site. Pre-approval inspections are done at the site of manufacture for all Class III devices, as are BIMO inspections.

The BIMO inspections ensure that samples were collected appropriately and data integrity of the submission has been maintained. For Class II these inspections are not required, and 510Ks also do not require annual reports.

When is down-classification appropriate? Class III devices can be down-classified to Class II when the risks can be mitigated with special controls in order to reasonably assure safety and effectiveness. In order to

consider reclassification we must first determine what are the risks to patient health should there be an inaccurate test result.

A false negative test result, such as with an antibody test or a diagnostic RNA test, may mean that the patient may not receive additional follow-up testing and be linked to care. The doctor may also pursue other etiologies. A false positive test result may lead to additional unnecessary testing procedures and psychological stress to the patient. A false low or high result may contribute to changes in patient management. These risks will be discussed further in this talk and in the next talk.

Special controls, since we've been talking about them a lot here, are statutory requirements for Class II devices. For potential special controls we have the ability to specify what the labeling should contain. We can ask for specific manufacturing information, method comparison studies, analytical studies, clinical performance studies and even post-marketing studies. Each of these will be described subsequently; however, please note that these do not represent all possible special controls.

Now I will tell you a little more about the serology tests. As Dr. Kamili presented, the CDC recommends

the following testing algorithm for identifying HCV-infected individuals. Testing begins with the HCV antibody test and then, if reactive, follows with an HCV RNA test. Thus, anti-HCV tests represent a first line diagnostic to identify HCF infections. Patients will typically not receive further testing for a non-reactive antibody result unless they are suspected to be in the early stages of their infection or have risk factors.

There are currently nine approved tests, one of which is no longer marketed and not shown here. The eight marketed tests have high performance for positive percent agreement ranging from 97.9 percent to 99.9 percent. They all share an intended use which has the following elements.

The test is for the qualitative detection of antibodies to HCV in human adult and pediatric serum and plasma, venous whole blood and/or finger stick whole blood. Assay results, in conjunction with other laboratory results and clinical information, may be used to aid in the presumptive diagnosis of HCV infection in persons with signs and symptoms of hepatitis and in persons at risk of HCV infection. The test does not determine the state of infection current or result.

The majority of marketed anti-HCV tests have the following minimum performance which is compared to a

patient infected status and that is determined by an antibody test result and an RNA test result with a sensitivity-positive percent agreement greater than or equal to 99.4 percent and a specificity negative percent agreement greater than or equal to 96.9 percent. Sensitivity and specificity are used when the test is compared to the clinical truth, and PPA and MPA are used when the test is compared to a predicate device.

I cannot emphasize enough that maintaining consistent performance across devices is important to FDA, especially in the context of device reclassification from Class III to Class II with special controls. This will come up again and is the single most important aspect of reclassification.

As previously mentioned, in order to consider reclassification we must first address what are the risks to patient health should there be an inaccurate antibody test result. For example, a false negative result may lead to the misdiagnosis of an infected patient. The patient may not be further tested unless they have risk factors or are in the early stages of their infection. This delay in diagnosis could impact the severity of the disease and mean that the individual may transmit HCV to others. Sources of

potential false negatives include interference and undetected device failure or lab error.

On the opposite side, a false positive result may lead to unnecessary testing and psychological stress to the patient. Sources of false positives include potential cross-reactivity as well as potential lab error.

The following proposed special controls are specific to anti-HCV tests. Dr. Schlottmann in the next talk will describe the proposed special controls specific for molecular tests and general for all tests discussed today. The minimum performance targets for sensitivity PPA of 99 percent with a lower bound of 95 percent, and specificity MPA of 97 percent with a lower bound of 96 percent.

We also propose the following labeling limitations which are already used in PMA product labeling such as non-reactive test result does not exclude exposure to HCV. Detection of HCV antibodies does not differentiate between acute, chronic or result infection. And, for lateral flow tests, the intensity of the test line does not necessarily correlate with the HCV antibody titer in the specimen.

Thank you.

DR. CALIENDO: Thank you very much. We are going to break for lunch and then we will come back and have -- Dr. Schlottmann, you have only been referred to 50 times this morning, so no pressure at all on what people's expectations are for your talk.

We will be back here at 10 minutes to 1:00. We will now break for lunch. Committee members, please do not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We will reconvene in this room at 10 minutes to 1:00. I will ask that all committee members please return on time. Audience members, please remember to take any personal belongings with you at this time. Thank you.

(Whereupon, a luncheon recess was taken.)

AFTERNOON SESSION

DR. CALIENDO: We are going to get started. Bryan has a few things to say before we move to our next speaker.

LCDR EMERY: For the record, I want to add two additional comments. Pursuant to the authority granted under the Medical Devices Advisory Committee charter of the Center for Devices and Radiological Health dated October 27, 1990, and as amended August 18, 2006, I appoint the following individual to serve as temporary voting Chairperson for the joint meeting of the Blood Products Advisory Committee and the Microbiology Devices Panel of the Medical Devices Advisory Committee on March 21 and 22. And that is Dr. Angela Caliendo.

For the record, this individual is a special government employee who has undergone the customary conflict-of-interest review and has reviewed the material to be considered in this meeting.

For the joint meeting of the Blood Products Advisory Committee and the Microbiology Devices Panel of the Medical Devices Advisory Committee on March 22nd, Patricia Lupole has been appointed to serve as temporary, non-voting patient representative. For the record, Mrs. Lupole serves as a consultant to the Anti-Infective Drugs Advisory Committee in the Center for Drug Evaluation and

Research. Mrs. Lupole is a special government employee who has undergone the customary conflict-of-interest review and has reviewed the material to be considered in this meeting.

The appointment was authorized by Dr. Rachel Sherman, principal Deputy Commissioner on February 13, 2018. Thank you.

Agenda Item: Molecular Tests for the Detection, Quantitation, and/or Genotyping of HCV RNA

DR. CALIENDO: We are going to move to our last formal speaker, which is Dr. Schlottmann from CDRH. She is going to be speaking about molecular tests for the detection, quantitation and/or genotyping of HCV RNA.

DR. SCHLOTTMANN: Hello. I am Dr. Silke Schlottmann, premarket reviewer in the Division of Microbiology Devices, and I will be presenting to you today about the molecular tests for the detection, quantitation and/or genotyping of HCV RNA.

As Dr. Garcia mentioned in her presentation, knowledge is an important component of device classification as it can mitigate the risk of uncertainty with respect to the device technology, device performance or even the disease itself. As you can see from this approval timeline of HCV tests, CDRH has about an 18-years long regulatory history with these devices.

Since the approval of the first diagnostic tests for HCV in the early 2000s, the field has rapidly evolved and the HCV tests have greatly improved in performance, specifically with respect to HCV RNA tests. Based on this long experience, CDRH, on its own initiative, is proposing to reclassify HCV tests from Class III to Class II.

As the title of this presentation indicates, we have approved three different types of HCV RNA tests -- qualitative HCV RNA tests, quantitative HCV RNA tests, also called viral load assays, and genotyping tests. There were three qualitative HCV RNA assays approved for strictly a qualitative claim, and only one of those is currently still marketed.

Five tests were approved for the quantitation of HCV RNA and four of them are still on the market, and two tests were approved for the genotyping of HCV. Each of those three HCV RNA tests comes with its own challenges with respect to validation.

I want to emphasize that FDA considers for reclassification only those HCV RNA tests that are *in vitro* diagnostic devices and regulated by CDRH. Tests used for blood screening purposes are not considered; they are separately regulated by the Center for Biologics.

I will now go through the intended uses of each of those three RNA tests. The qualitative HCV RNA tests are used as an aid in the diagnosis of active infection by qualitative detection of HCV RNA in serum or plasma. The tests are indicated for use only in individuals who are antibody-positive for HCV as the detection of HCV RNA is evidence of active infection, but it does not distinguish whether such an active infection is acute or chronic.

The early viral load tests were marketed solely for quantitation of HCV RNA and were intended for use as an aid in the management of HCV-infected individuals undergoing antiviral therapy. This means they were only used in patients who were already determined to be HCV antibody and HCV RNA positive. As such, the early viral load tests were validated only on specimens from individuals with established active infection, but they were not validated for populations without prior diagnostic history of HCV RNA, which we call the diagnostic testing population.

In addition, the early viral load tests include in the intended use that the test measures HCV RNA levels at baseline and during treatment and can be utilized to predict sustained and non-sustained virological response to HCV Treatment. The reason for the inclusion of the second

element in the intended use is that the early viral load assays were approved based on clinical utility studies with patients on the old interferon-based treatment regimens which used the viral load at specific on-treatment time points to define rapid virological response, or RVR, and/or early virological response, EVR, in order to predict SVR.

Recognizing that in clinical practice HCV viral load tests had started to be used off-label for diagnosing the active infection, FDA has actively encouraged developers in the past about five years to also validate the viral load assays for diagnosing active infection in HCV antibody-positive individuals with unknown RNA status. This led to the approval of three viral load tests that were validated with both populations of HCV antibody-positive individuals, those with unknown RNA status, meaning those for whom it was unknown whether or not they had an active infection, and those who were known RNA positive, meaning they were previously diagnosed as actively HCV infected. Consequently, these assays have an intended use claim for both as an aid in the diagnosis of HCV infection and as an aid in the management of HCV-infected people undergoing viral treatment.

The third type of HCV RNA tests are the genotyping tests for HCV. They are intended for use as an

aid in the management of HCV-infected individuals, and in guiding the selection of therapeutic treatment indicated for those specific genotypes that were validated in the analytical and clinical studies. And the genotype tests can differ in the kind of genotypes that were validated in those clinical studies. Furthermore, the assay is intended for use on patients who are chronically infected with HCV and who are being considered for antiviral treatment.

As we heard earlier this morning, when considering reclassification of HCV tests, FDA is taking into account the probable health benefits and the nature and known incidence of the risks associated with the use of these devices. Despite very good performance of HCV tests, the severe consequences of a false positive and false negative result to patient health and to public health for them present a substantial risk.

False negative results can lead to the misdiagnosis of an actively infected patient as one that has cleared or resolved HCV infection. Consequently, a patient may experience a delay or failure to identify active infection and linkage to the appropriate care, a delay and/or failure to perform appropriate additional diagnostic testing procedures such as the assessing of the severity of HCV-associated liver damage. It may lead to

unnecessary testing in pursuit of another potential cause of hepatitis and, very important for public health, it may lead to the transmission of HCV infection to others.

In the context of HCV viral load tests, a false negative result can also incorrectly determine SVR when the patient is still actively infected, with similar consequences as the one I just mentioned such as the delay or failure to link the patient to the appropriate care and the transmission of HCV to others. Sources of false negatives can be a too-high limit of detection of a test, the genotype inclusivity of the test, interference, and then, while we all strive for perfection, no device and no human being is perfect and, therefore, with a lower likelihood due to either an undetected medical device failure or human error. A diagnostic test will occasionally give a wrong result.

HCV RNA tests have also risks related to false positive results which can lead to the misdiagnosis of a non-infected person as one with active HCV infection, and that can cause unnecessary diagnostic procedures such as viral load testing and genotyping. In the context of the new generation viral load tests, a false positive result can also lead to unnecessary treatment as these new viral load tests determine the active infection but also provide

a viral load result. Hence, these tests omit the need for the second test within the traditional CDC HCV testing algorithm. Social concerns and psychological distress to the patient should also be considered.

Of note is that, in the era of direct-acting antivirals, falsely elevated or too low viral load results are less concerning because response-guided treatment based on RVR and EVR are not currently used anymore. This would, however, be a concern if response-guided treatments would become relevant in the future with any kind of new drug.

Sources of false positive results are cross-reactivity and undetected device or laboratory errors, as discussed in the previous slide.

For genotyping assays, the risk pertains to an incorrect genotyping result; for example, somebody who would be genotyped as genotype 1 when the patient is really a genotype 3. An incorrect genotype can lead to potential incorrect choice of anti-HCV regimen with respect to the kind of drug and the specific treatment duration, an increased risk of emerging drug resistance due to the sub-optimal therapy, and the exposure of the patient to the potential adverse effects of alternative regimens.

Sources of incorrect genotype results can be cross-reactivity, microbial interference and undetected device failure or laboratory errors.

All currently marketed HCV RNA tests have good performance. The diagnostic and viral load tests have an LoD that is below 20 IU per ml, and they have positive and negative percent agreement of equal or above 98.5 percent. For genotyping assays, the genotyping rate is equal or above 90 percent and the genotyping accuracy is equal or above 98.5 percent. The genotyping rate refers to the proportion of valid genotype results that are interpretable and the genotype accuracy refers to the proportion of interpretable results that match with the result of the reference method.

As Dr. Garcia pointed out earlier, FDA's main concern regarding reclassifying HCV diagnostic devices from Class III to Class II is to maintain this high performance, to maintain it consistently across different devices of one type, as well as to ensure consistent performance of an individual device throughout its total product life cycle, or TPLC.

In the context of consistent high performance, FDA realizes that throughout a product's total life cycle the product usually undergoes various changes. While these

changes in the majority of cases are made without the intention to alter the product's performance, a lot of those changes have at least the potential to impact the performance and, hence, the safety and effectiveness of the device. The potential impact on safety and effectiveness is for the manufacturer to assess; however, FDA has experienced that a correct assessment can be tricky and oftentimes correlates with the regulatory experience of the manufacturer.

As Dr. Gitterman pointed out, there are existing FDA guidance documents that have actually recently been updated which help manufacturers assess when to submit a new 510K for modifications to an existing 510K device. The guidances are referenced here and below.

Per guidance, changes in technology, engineering, performance or materials that might alter the operating principles of an *in vitro* diagnostic device would likely require a new 510K. As described in these guidances, especially in the first one that is referenced here, these include critical components such as antigens, antibodies, primers and probes, mainly those reagents that give a device its analyte-specificity.

The risks to health, including FDA's concern that high performance is consistently met, need to be mitigated

when we reclassify HCV diagnostic devices. One way of doing this is through the implementation of special controls. Special controls, as we heard this morning, are measures added to the general controls to mitigate risks associated with diagnostic devices. And, as a reminder, the general controls apply to all medical devices regardless of the class and exempted status.

Special controls are special because they are device type-specific. For HCV tests, we proposed special controls that anchor around four main areas: analytical studies, clinical studies with pre-set performance criteria, selected design control aspects and selected total product life cycle controls. I will go through those special controls in a bit more detail now.

Regarding the analytical studies, as Dr. Garcia pointed out, we do not see any major changes in comparison to what we are currently asking for for our PMA products. We have consistently used the WHO international standard material in our viral load and diagnostic HCV RNA tests. It is a reliable standard material derived from human material. We will continue asking that these tests be made traceable to an acceptable standard or the WHO standard. We will also continue to ask for metrics of the sensitivity of the assay such as LoB, LoD and cutoff, as well as

linearity, cross-reactivity, interference, precision, reproducibility, accuracy sample stability and reagent stability.

In this table you can see the performance of the currently marketed qualitative and quantitative HCV RNA tests. The genotyping assays are not listed in this table. For all these tests, the LoD is below 20 IU per ml, and you can see that positive and negative percent agreement between 98.8 to 100 percent for PPA and 97.9 to 100 percent for EPA. Of note is that PPA and NPA only applies to those tests that also have a diagnostic claim. Viral load tests that only have a quantitative claim are assessed based on their clinical utility to predict SRV, and, hence, sensitivity and specificity of PPA and NPA are not used.

Based on the performance of currently marketed tests, FDA has developed clinical performance criteria that we propose to include in the special controls for HCV devices and which would have to be met by any new device that comes in at the time of clearance and, also, thereafter. For diagnostic and viral load RNA tests this would be a PPA of 99 percent and an NPA of 98.5 percent, both with a 95 percent confidence interval, a lower bound of the 95 percent confidence interval equal or above 95 percent. For genotyping tests, this would be a genotyping

rate of above or equal to 90 percent and a genotyping accuracy of above or equal to 99 percent.

Because these performance goals are currently met by the marketed devices, FDA does not expect that meeting these goals represents a major issue for future devices.

In addition, FDA considers to specify various other special controls which we will harmonize as much as possible with those special controls that the Center for Biologics would have liked to discuss with you for HIV yesterday. As Dr. Garcia pointed out, please note that the special controls discussed here are not all-inclusive and that there may be the need to add or remove special controls in the process of reclassification to mitigate the risks discussed today.

The special controls we are considering include a detailed device description in which all components of the device that the manufacturer considers critical should be specified. FDA considers this information crucial to understand individual devices and to properly assess the risks associated with each of them.

There will be labeling mitigations as currently used for our PMA products such as limitations regarding non-reactive results, and this is targeted towards the window period; warnings with respect to specific

populations for which the test was either not validated or can reasonably be expected to have an increased risk of false results such as immunocompromised or immunosuppressed individuals; warnings pertaining to non-validated uses of the device or uses that fall into the purview of other FDA centers such as blood screening devices, which I previously mentioned are regulated by the Center for Biologics.

As pointed out before, we are concerned about changes throughout the total product life cycle and consistent performance. Examples are design aspects such as final release specifications as well as shelf life and the acceptance criteria for stability. We would therefore like to see that these aspects will be addressed in the special controls.

The reclassification of a device from Class III to Class II is dependent on the extent to which special controls, along with the applicable general controls, are sufficient to provide reasonable assurance of safe and effective use of the diagnostic device. Therefore, the question to the panel today is whether the panel members believe that the risks associated with the following HCV tests can be mitigated through special controls: anti-HCV tests, quantitative and qualitative HCV RNA tests, and/or HCV genotyping tests.

Note that risks refer to not only the risks we presented here but also to any additional risks you may be aware of. If there are any such additional risks that you may be aware of, we kindly ask that this is brought to our attention during the panel discussion. Please include in your deliberations a discussion of whether the panel believes that certain modifications to the design of the device, such as stability or final release criteria, would be likely to significantly affect the performance of the device and, as a result, its safety and effectiveness.

Our division director, Dr. Scherf, has thanked all the individuals and I want to extend my thanks.

Agenda Item: Questions to FDA

DR. CALIENDO: Thank you. That was very helpful. We are going to have some time now for questions to both of the FDA speakers. And I think if you have questions for any of the speakers this morning I am sure they would happy to accommodate.

My general question is I don’t feel like I have enough information on special controls from a post-marketing perspective. I understand that analytically the requirements are going to be the same. You have a lot of special controls regarding clinical studies and labeling and all that. Now the product is approved or cleared. Can

you help us understand what final release criteria area? Stability criteria I assume is how long does it stay on the shelf and still function.

But what I'm trying to get my head around is what is the risk -- What is the difference between a PMA and a 510K when it comes to what you do after the test is approved? What is going away because it is no longer a PMA, and what could we then request as a special control to make sure that that was accounted for?

DR. SCHLOTTMANN: The difference -- and I think Dr. Garcia alluded to that earlier -- Ror example, with respect to final release criteria, for a PMA a change in final release criteria would need to be submitted as a post-approval supplement, a PMA supplement, to FDA and we would review that. Under the 510K, this would not be the case any longer.

So, a manufacturer can change the release specifications, and just for those who don't know, they are set by the manufacturer in order to make sure that consistent performance is met or a certain pre-specified performance is met for the device. These could be changed for a 510K but would not need to be submitted for FDA review under the general 510K paradigm, unless we address this with special controls.

DR. CALIENDO: Could you give us some examples of what final release criteria are? That’s not the sensitivity and specificity of the assay?

DR. SCHLOTTMANN: That could be part of it. It really is up to the manufacturer to set final release criteria. They could, for example, use a panel of samples and see that they were correctly detected. Or, for those that quantify the viral load, they may have certain panel members that will be tested before they release a lot, and then a certain viral load for those panel members would need to be met, plus/minus, obviously, a certain safety margin due to the reproducibility of testing. Those would be final release facts set by the manufacturer.

And the same is true for stability. There is an initial shelf life testing that manufacturers perform in alignment with the testing and the pass/fail criteria that a company would set for such a study. They would set their final release criteria based on the passing time points on their study, and, yes, this would be the shelf life. Any extension of the shelf life would need to be validated, but the manufacturer would usually, under the 510K paradigm, keep those records on file in their facility. Those would not be reviewed by FDA.

DR. CALIENDO: So, asking a company to have the FDA review that, is that burdensome to the company and to the FDA? Having substantial changes to the release criteria -- are these things we could ask as special controls?

DR. SCHLOTTMANN: Usually, if we address that in the special controls these would be information that the manufacturer is expected to have gathered and have on file anyway. The only difference could be that we may now review it or not. It depends on how we would address this in the special controls.

MR. SPRING: Brad Spring. I just want to comment on your question regarding industry and the burden.

I think having release criteria to have to be reviewed by FDA before implementation is a burden more on the time. I don’t know how long it would take. But I think, instead of doing our validations, changing the release criteria and then releasing the product, we would add in the step of preparing a submission with whatever fees are associated with a submission and having FDA review it.

DR. CALIENDO: It would be a resubmission if we said the FDA had to review it.

MR. SPRING: Potentially. I would say there are some things in the PMA world that you can implement -- very few -- but you can implement without FDA’s approval. You

typically put those in an annual report. But the majority of changes would require FDA review before implementation.

DR. GITTERMAN: Just a quick point. As Dr. Schlottmann pointed out, there are two existing FDA guidances which are very clear about when a new 510K for a Class II device is requirement. To sum up 39 pages in one sentence, significant changes to the device do require a new 510K.

The question, of course, is what are significant changes. Again, companies do a very good job. Part of what Silke is saying is that, in the nature and significance of hepatitis and the benefit-risk, FDA is somewhat defining -- and again it's in your packet -- a few specific areas that we think reflect significant changes such that we would want to at least see what the validation is.

Mr. Spring's point is very well taken, and perhaps there should be some thought to how we implement it. But this is a way to define and aid the company as saying this is what we think *a priori* will always be significant, so we don't want it to be subjective.

There is also another guidance in the modifications to devices guidance which also states that if, in fact, it is in the special control, they have to come in. It's not like this is something new we're putting

in. What we are doing, though, is trying to define the circumstances in the guidance that would require coming back to us with a submission.

I do think the point is well taken and we would have to think if there is a less burdensome way to do it that would not require the full industry clock for that. I think all the points are excellent.

DR. KIMBERLIN: I believe you said that each of the tests already approved do meet these criteria on this table?

DR. SCHLOTTMANN: Yes. There is one that falls a little short.

DR. KIMBERLIN: Yes. And the same is true with the antibody test, the same statement was made, but at least to my viewing it didn’t quite line up. So, if there is an inaccuracy there, are you proposing that this gets kind of grandfathered in or rounded up? How does that match with your statement that they all qualify?

DR. SCHLOTTMANN: Yes, in this case, we would round those up. I want to emphasize that these tests would not be removed from the market, if that’s your concern.

The other thing, with respect to this first gen probe assay -- this is, I think if I am not mistaken, the oldest assay that we have out there, so all the recent ones

actually would meet that criteria. Also, the performance is based on a slightly different clinical study -- I don't want to go into detail there -- than our other assays, so we would not expect that to be an issue to meet this performance.

DR. KIMBERLIN: If I saw it correctly, on the serologic tests there was a similar product that didn't quite make it. You are not looking to propose that that get taken off the market either?

DR. SCHLOTTMANN: No. Just to expand on that point, there is always the risk-benefit for each individual device. So, even if a device would fall short, it really depends on the exact intended use because that is driving our risk-benefit analysis, and that may leave room to work with manufacturers that are maybe not quite meeting this bar. But I do want to emphasize that this is a target that we really want our assays to reach.

DR. THOMAS: Dave Thomas. Thanks for that presentation and those comments. I am going to follow on that same line of sensitivity and specificity and ask to what extent does need factor into the determinations for these thresholds?

For example, I think most of the clinicians would agree that what we have right now worked perfectly well for

taking care of patients. What we need to solve is the inability to confirm infection at the point of care since one-half of the people, as Dr. Ward pointed out, who are tested positive by the screening test never get to have their confirmatory test done.

So, at a population effectiveness level, a test that only incrementally improved the confirmation at the point of care could suffer, could have much less sensitivity and still have many more people end up being confirmed with their infection if you counted all those that failed to come for a confirmatory test in an intent-to-treat way as a failure of that test scheme.

I realize that life is not that simple and you can’t always test things in real population settings, but I am only saying that to ask, with other examples like maybe point-of-care pregnancy tests or other tests that you push out to the point of care, why have the same high -- not that I would ever want to be a proponent for something not being accurate as possible, but certainly would be personally willing to sacrifice a bit on that -- like the gene expert data that were shown were about 98 percent, but every single person in that drug use van got confirmed.

So, looking at it from my perspective, that was a pretty important paper and a pretty important breakthrough,

but they wouldn't have gotten approved because it was only 98 percent in their first study, and in the second one, as was mentioned, it was 100 percent. But just to use that as an illustration, would that have failed by this new rigorous standard?

DR. SCHLOTTMANN: First, these special controls that we put forward today are proposed, and we really invite the panel to discuss those things that you have just brought up, because this is obviously something that we would also consider. It depends a little bit on the technology of the assay. We are aware that there are certain technologies that may benefit the patient but might not get quite to the performance level that we are used to seeing in laboratory-based tests, so this would all go into the benefit-risk analysis for certain devices. As I said, it would be good to discuss those things and, also, performance goals that the panel believes would be appropriate.

DR. GITTERMAN: We are not discussing a combination test on the table right now. I think, as a starting place, there is a sort of general need that we don't want to lower the bar. However, I can certainly conceive of it exactly as Dr. Schlottmann said. One is that a different intended use could have a different benefit-

risk, especially if there are mitigations. I suspect that for testing for HCV we would sacrifice specificity for sensitivity because the risk of a false positive on the grand scheme of things is far less than the risk of a false negative.

So, again, I would appreciate your opinion. That could fit into the benefit-risk. Again, one could argue in a lot of ways that a point-of-care test, et cetera would be beneficial.

But as long as there is a mitigation -- Right now, I can't remember if it was Dr. Kimberlin who said were we considering lowering of the bar. Certainly we are not considering taking anything off the market; we want to maintain the bar. Bur again, if there is an overwhelming clinical need -- and we always have access to experts to get input on the decisions we make -- we might have to consider it.

So I think the point is well taken, but I don't think we're discussing this right now in the context of the kind of tests we're discussing.

DR. CALIENDO: Steve, I don't know if I am allowed to say this, but this is exactly what was proposed for HIV, that the point-of-care testing and the lab testing would not have the same sensitivity and specificity. It was

slightly lower. It was 98 versus 99. So, is that something that would apply here?

DR. GITTERMAN: That could well be considered given the circumstances. But that took four advisory committees and I don’t know how many years of discussion.

DR. CALIENDO: Might as well leverage the fact that they were successful.

DR. GITTERMAN: Usually, when you say something, when somebody prefaces the question with “I’m not supposed to say this,” the answer usually is no. So if anybody is thinking that, she has the prerogative as the chairperson.

DR. STAPLETON: I have a clarification question about mitigation. It was alluded to in Dr. Schlottmann’s talk that this has not been validated as a diagnostic test for nucleic acid testing, but I think we all agree it probably will be used in that way in many settings. So, from a mitigation standpoint, since we won’t have necessarily, right away at least, data to support that, does mitigation mean that there will be a clarification that this is not approved for this use? Is that what you mean by mitigation?

DR. GITTERMAN: Yes. That is almost exactly right. There are many ways to do so. But I would caution the committee that some of the discussions revolving around a

device that is not clear, that we have not seen or approved -- I'm sorry, the PMA is approved, and in fact, when you get to 98 and 99 percent performance, there's a lot of the devil is in the details about why people didn't do it. Again, Dr. Thomas could discuss this. When you take an intent-to-treat approach, the HCV drugs don't do that well because people don't take their drugs, and depending on whether you put in the qualification that people took drugs or not. So, again, we're talking about something I don't think anybody has read in that great detail.

I would never say we are very liberal. We are very rigorous, but we are also very reasonable. Again, not having read that paper carefully, I think we are not in a position to discuss what's 98 or 99 or 96 if they toned it up a little bit. So I would be careful about saying that this is a known quantity.

There's a lot of the devil in the details. If a test is 50 percent, not too many people are going to care about two or three percent. If you are 98 percent or 99 percent, then it's not very many patients to make a terrific difference.

DR. STAPLETON: I agree about that 1 percent, but I guess my question is, if these are at 99 percent and

they're approved, they will undoubtedly be used in that setting that we don't have the data for.

DR. SCHLOTTMANN: If I may clarify, what I heard in your request for clarification is that you were under the impression they were not approved for a diagnostic population. Did I hear that right?

DR. STAPLETON: That is what I understood earlier.

DR. SCHLOTTMANN: Three of those assays that you actually see in this table do have approval for both a diagnostic claim and a viral load claim, so they are validated with both the diagnostic population with unknown RNA status and the ones that were actively infected.

DR. STAPLETON: So that would be more guideline issues than approval issues.

MR. SPRING: This is more of a comment and is directed towards FDA. I am not sure if everyone on the panel is familiar with the CLIA waiver process, where, in the conversations and the pre-read, one of the important aspects of down-classification is going to be access, and access, to me, is in the point-of-care office.

So there is an extra step, so to speak, that manufacturers have to go through to be able to validate this test, whatever it may be, for use in that setting.

Could you maybe just describe that a little bit? I didn't want to over-complicate the conversation.

DR. GITTERMAN: It is a very important point and we could discuss it for half an hour. It's a complicated issue. But again, as Dr. Schlottmann and Dr. Garcia said, it is all benefit-risk, and we could all invent different things.

I would suggest, but again, others may disagree, that sensitivity is going to be much more of an issue than specificity. But as Dr. Ward and Dr. Kamili were pushing, if you had a combined HCV antigen test and antibody test that would go a long way to mitigating some aspects, because not only would it serve as a confirmatory test but it might serve as a separate diagnostic test.

We would have to look at this individually. There is nothing prohibiting CLIA waiver in anything that we are talking about under a Class II product. And again, I think the analogy to HIV is very important.

But I do think we have seen superb performance to date, and balancing these issues, certainly, if somebody came in with an exceptionally well performing CLIA product that met these guidelines, everybody would be thrilled and no one would rule it out.

I would suggest when we get to this level of performance, which is really very, very good -- and Dr. Miller made the comment we're talking about laboratory errors and handling errors, and they probably have overcome the inherent error in the test itself.

DR. SCHERF: There is one additional aspect that might not be clear to everybody. If you go into a clear waived environment then you have to demonstrate the test with certain simplicity. The ones that we are discussing today are not necessarily all of that type.

I think the other part is, in order to then obtain the clearance approval for a point-of-care or the clear waived setting, it really then requires additional testing of non-trained individuals. So again, I think what we are talking here about is these laboratory tests that have extreme high performance and we would like to have the panel deliberate whether we should consider down-classifying them to Class II.

The other tests, as Dr. Gitterman said, can be evaluated, but I think a new risk profile and risk evaluation is needed in order to really move forward with those types of tests.

DR. LEWIS: I have a couple of questions. I would like to first go to slide 18, the next slide. Why is there no lower bound listed for the genotyping test performance?

DR. SCHLOTTMANN: In part because some of the genotypes are not very frequent in the US, like everything above three. Genotype 4, 5 and 6. So, getting the sufficient sample numbers for those assays is a problem, which is why we can't set a lower bar because you would need so many samples to meet a lower bar, let's say, of equal or above 95 percent that it's not feasible.

DR. LEWIS: Okay. But for common genotypes you could set a lower bound.

DR. SCHLOTTMANN: We could, or we could set a combined goal.

DR. LEWIS: But you could consider, for example, having a genotype-specific lower bound as opposed to remaining silent on it.

DR. SCHLOTTMANN: Potentially. I would say the more feasible way to go is to have a combined goal because, really genotype 6 and genotype 5, the samples are so few that any kind of goal would not make sense.

DR. LEWIS: Let me try again. You could set a lower bound for genotype 1.

DR. SCHLOTTMANN: Yes.

DR. LEWIS: Okay.

DR. GITTERMAN: We could set a lower bound for anything. It's just the number of samples you get.

DR. LEWIS: I understand that. The argument against setting a lower bound for the most common genotypes, which is obviously the test result that affects the largest fraction of patients, was not very convincing, so I would strongly suggest that you set a lower bound. And it's completely fine to set it for genotype 1 -- whatever are the common ones.

Could we go to slide 21? I am trying to understand what the panel is being asked. I didn't hear anything about CLIA waived in the questions, for example. We are being asked whether we think that the risks associated with down-classification from III to II could be mitigated through special controls. Sort of a yes/no question.

The way I heard the question, it sounded as if we are being asked to make that determination without having to be exactly specific about what those special controls could be. It's kind of a hypothetical; do we think this is possible. Is that right?

DR. SCHLOTTMANN: Yes. There were a few special controls that were discussed such as the labeling

mitigations for specific populations on uses, for example, certain limitations for assays.

DR. LEWIS: I understand that, but I am looking for the logical structure of the question. The question we are going to be asked to vote on is do we think that special controls could be used to adequately mitigate the risks of down-classification.

DR. SCHLOTTMANN: Correct. But under consideration of what we suggested here, such as the performance bars for clinical studies.

DR. LEWIS: So that is my next question. Okay. Are we going to be asked -- I will turn to the Chair and designated federal official. Are we going to be asked separately whether or not we support or suggest a modification to the specific, for example, performance criteria given in slide 18 as those special controls?

DR. CALIENDO: Yes. When we are done with public comment we will continue discussion, and then everyone will have an opportunity to comment on what they would consider or what advice they would like to give to the FDA regarding special controls.

DR. LEWIS: Okay. But that is advice; it is not a voting question, because voting questions have to be pre-specified, correct?

DR. CALIENDO: Right, and we are not voting today. Right.

DR. LEWIS: We are not voting at all today. Okay. My mistake.

The question about this risk-benefit, the thing that struck me also about slide 18 is those are performance criteria. That is not a risk-benefit assessment. The assumption is, if I understand correctly, that if you went forward with a down-classification and the agency wrote a set of specific controls that were the general approach to risk mitigation in this setting, the agency would retain the flexibility to work with manufacturers who were proposing a product that might be used in a different setting, might have greater access or other considerations to approve a device as a Class II device with lower standards than the general standards if the risk-benefit assessment was deemed favorable by the agency. Is that correct? So you don’t lose any flexibility.

DR. GITTERMAN: That is somewhat correct, and let me be clear. What we are talking about are the type of devices we have seen to date. We can look through history, we can look at what has been done and say this is exactly for this case. We cannot say for the type of device that’s sort of being thrown around what that device is, what

exactly would it look like, what the performance would be in that case. So, yes, we have some flexibility but we are not proposing a tremendous amount of flexibility.

Now, if I could go back to the earlier point, it is always benefit-risk. Dr. Schlottmann and Dr. Garcia went through some of the risks, and I think around the table we have tremendous experts, I hope there are people with experience, and I would have to say I think almost everyone in the room has been touched either professionally or personally by hepatitis-C, and I think there is a general sense of what the risks are.

The point is, in the setting of these special controls given what we all understand the risks to be, would it be acceptable to reclassify it from Class III to Class II. But some of the possible uses which we don't know about, different intended uses, again, we would have, one, some flexibility, and, two, we certainly might want to look at different mitigations, how exactly that device is going to be used.

Again, without going into great detail -- let's say a combination device where one risk balances the other so you'd say, look, I have two tests that, one, might be completely independent and, two, both have very, very high performance -- together like an antigen and antibody test -

- even though -- I should not be mentioning antigen at all -- that might accept slightly lower performance from the antibody side if the sponsor could show that, yes, it still picks up overall the same percentage of people.

That's a long-winded way of saying we are reasonable but not that reasonable. Within limits, we want to maintain very high performance. This has been considered previously a significant enough disease to warrant Class III status, as HIV was, and can we down-classify this reasonably by at least making sure on the product side all these things are addressed. And a couple of post-marketing aspects, which I know will be discussed further, and labeling mitigations that would ensure safe use.

As Dr. Scherf said, we are not discussing CLIA waiver, but CLIA waiver would involve a new set of testing and a new consideration of mitigations and potential risk. Because it is not going to be done by ID docs or hepatologists or, even now ASLD wants to push it down to general practitioners, which is fine as well.

DR. ADEYEMI: Just following up on Dr. Thomas' comment that the diagnostic accuracy of the test is only as good as the patient actually getting the test. It is important to see slides like Dr. Saleem Kamili presented looking at that data with doing the testing on the same

sample and looking at cross-contamination. I guess there is only one of those equipments with the fixed probe, so that is comforting.

But also the point that was made by Dr. Miller about -- again, in our system it is done by chemistries. It is automated, it is run through, it’s out in 30 minutes, and then micro does the reflex test on the same sampling, and so being able to look at some of that data for all of those diagnostics.

Also, as we go outside of the risk-based testing and the birth cohort, if we eventually get to where we have mass population screening and we get to lower prevalence, we have got to figure out when the prevalence changes and the predictive value of some of these tests are going to change and what that means, because we are going to be doing reflex testing on a lot more false positives.

DR. GITTERMAN: Just to address the first part of your point -- and I am sure Dr. Schlottmann can comment better -- cross-contamination is a standard part of evaluation of every test and is done very thoroughly. I thought the presentation by Dr. Kamili was excellent, but there is no test that gets out the door with a lot of cross-contamination.

Again, CLIA keeps coming up, but when it goes to that level there is a large number of flex studies as well as cross-contamination studies that are done. It's a standard part of every evaluation, be it PMA or CLIA, and especially when we're talking about nucleic acids. Contamination doomed nucleic acids until about 2000.

DR. SCHLOTTMANN: The only thing I want to add is that the tests we are currently discussing are having intended uses that are based on populations with either signs and symptoms or risk factors, so this is what we consider for reclassification.

If we are now talking a different population, a broad screening of people that have no signs or symptoms and no risk factors, that would not be covered under the current reclassification efforts, and we would need to re-think how we would want those assays to come in and what the benefit-risk is. We would also need to re-think performance goals in this context.

DR. CALIENDO: From a public health benefit perspective, when I think of the risk-benefit, we have been talking on and off about getting the test to the patient population that needs it. Down-classifying opens the door for manufacturers to bring innovative and creative things to the table. That is at least the way that I look at this.

If we can make sure that the performance characteristics are okay -- and it's interesting to know that the analytical requirements are identical -- we could open the door for access to testing by manufacturers having a lower regulatory burden to bring an innovative, near patient point-of-care combination, whatever it is, to the market.

DR. GITTERMAN: I think you have read Dr. Lathrop's slides from the previous day, because that literally is word for word what she would have said. Again, I am by no means suggesting what FDA's opinion is, but one of the hopeful aspects of reclassification we hear constantly -- and I am sure Mr. Spring could comment better from companies based abroad or small companies -- that the PMA is a hurdle such that small startups or investment companies or companies abroad see that as such a challenge that they do not wish to come to the FDA market.

Again, without discussing things we are not really dealing with, but the hope is even within the space that we have now -- and Dr. Schlottmann's discussion of that award release -- hopefully, innovative approaches and different ways -- I'm going backwards, from the premise that you had, but -- that could be used in other settings,

so to speak, and give certain benefits to public health we don't have now.

DR. CALIENDO: My question is you have given us the question; do you want us to give you thoughts on special controls, reaction to your proposed special controls and other things that have come up through the course of the discussion or that will come up through the course of the discussion?

DR. SCHLOTTMANN: In general, yes. If something comes to your mind that may not have been addressed in one of our slides, we don't want to get lost in the detail and how the special controls would be worded and how very specifically they would look, but the general ideas would be very welcome.

DR. CALIENDO: I would like to come back to something Dr. Dodd asked earlier today, which is can you put special controls around the predicate devices so that they are required to use the highest performing predicate device or a higher performing predicate device so that we don't go down this slippery slope? Is that appropriate, or does that just show too much favoritism to one manufacturer over another?

DR. SCHERF: Yes, that is absolutely correct, you can do that. I think we have done this also with other

products that we are working in the flu environment where there were different predicate devices available. I think what you described, the slippery slope, is a concern that needs to be addressed.

But with the wording and with the special controlled approaches, that can be covered in a way that you can even mention that the predicate device needs to be a high performing FDA CLIA device suggested or recognized by FDA. So these approaches are available that allow us to really avoid the slippery slope occurring in the future.

DR. WARD: I just want to get back to something, Angela, you touched on, which is let’s keep the problems that we are trying to solve in mind. We talked about the high proportion of people who don’t get the confirmatory test to actually diagnose their current infection. How can this help with that?

We know that people who are at risk for hepatitis-C often are very marginalized populations and we have to do a lot of testing in outreach settings -- drug treatment, syringe exchange, correctional settings, et cetera. How can this help with that type of issue as well?

As was brought up, if we do want to go to mass screening, again, how can this type of downgrading help with that, and what kind of controls can be put in place?

For example, you want to have a little bit different quality criteria for a screening test but then have quality control as I understand it where you could say before a therapeutic decision is made this must be followed by a more rigorous X test, whatever you want to say. That way, you can help solve one of those problems.

I would like to encourage the committee and the FDA to keep the problems we're trying to solve in mind.

DR. GITTERMAN: I think we could all accept the fact that the committee is very concerned about the screening and the larger use of an assay that would be easy to use, exceptionally reliable, et cetera. I unfortunately fear that that may be the subject of another meeting because the technologies we're talking about are not applicable for this situation. I don't think any of the moderately complex technologies are ready to be adopted immediately to large-scale screening at a CLIA-waived site.

However, the point I think is loud and clear that if such a device were to come to us and if it had a tremendous ease of use and some level of performance that, on a public health basis -- we are not going to ask you back, though (that's a joke) -- on a public health basis could be well justified on benefit-risk to do so, we would certainly entertain it. And I certainly think again that is

where numbers become critical as to what the bar would be, and we may ask to have the committee meet again, or, in fact, we might seek out information through other mechanisms we have.

But I think that is very well taken. I would hope that we could perhaps -- without telling you what to do -- more restrict this discussion to devices that are similar in technology to what we have now, recognizing that the work of this committee may spur a new type of consideration, and again, to emphasize more -- I have to apologize, I can't see the name card -- Dr. Lewis's point, which I think is very well taken, there is a lot of the devil in the details, and we would like to be flexible.

MR. SPRING: I don't want to belabor the CLIA waiver piece of this, but I think that's where these tests are going. The one test that is on here that's CLIA-waived is that Orasure test that you saw, and I don't want to call up the slide, but there were two results. There's one for venous whole blood that met the criteria of 99.5 percent on the point estimate but did not meet the criteria when you look at finger stick, and that is the test that's used in the point-of-care lab. I think we clarified that that is not going to come off market under the new criteria.

But I think it does dictate a discussion around point-of-care tests in the waived setting but also maybe the specimen type. When you look at finger stick whole blood, is that something that does need different criteria, because that is what's going to be used in these settings, most likely.

DR. GITTERMAN: That is a fair comment. I don't think we would want to go there because -- not to say you're obsessed with the CLIA-waived approach, but it is very important. Let me ask this. Does everybody understand what we're talking about in that context of CLIA waive? We don't want to get --

DR. KIMBERLIN: If you could explain, that would be helpful.

DR. GITTERMAN: Okay, and I hope other people will correct me. Basically, a test is approved for use in a moderately or highly complex laboratory in certain environments. To go to other laboratories, outpatient laboratories, what are called CLIA-waived laboratories -- it's a specific regulatory definition -- tests have to be CLIA-waived. The tests almost always that you receive in your doctor's office are going to be CLIA-waived. I won't go into over the counter which is a different area. But any test which is widely used outside classically where someone

would fully get your blood -- a lab core, Quest, anything like that -- will be CLIA-waived.

FDA recently cleared a version of the -- well, let's take Group A strep tests. Almost all of those are CLIA waived. What Mr. Spring is getting at is that CLIA waiver would, in fact, be one of the ways that would enable large-scale screening of the device; otherwise, it would never work if you were stuck to doing it in laboratories.

CLIA-waived collection devices are sort of a hybrid product. But in fact, CLIA waiver would mean you got the result and you performed the test at the point of -- Point of care is something different. If you were to do blood gas in a hospital laboratory, that is a point-of-care test under the auspices of the hospital laboratory. You could not take that same device and take it to your doctor's office. So point-of-care is separate from CLIA.

But if you are looking to have a test that can be done at every physician's office, that could be done in CLIA-waived facilities, that would be CLIA-waived. I think Mr. Spring correctly is making it virtually synonymous with the concept of doing widespread screening, as you're proposing. That would almost certainly be a CLIA-waived test.

I would not extend it, though -- and your point was -- into sample type -- the fact that they have this performance for a finger stick, et cetera -- because the performance of the test, the criteria, the way they studied it, is different.

But I would say absolutely we would welcome devices to come in that could meet CLIA-waived criteria. Again, our goal is to approve safe and effective devices, and on the basis of benefit-risk we will do so. And there is no prohibition -- we have CLIA-waived things that in my lifetime I would be shocked at. Again, as in the example of HIV, there are very good public health cases made for some of these things.

DR. MILLER: I just want to point out I think there's a disconnect here because the data that's being presented we were told is based upon patients with symptoms, not broad-based screening. How these tests are being used is for broad-based screening in I would say all of our institutions. From a laboratory perspective, we don't have control over which patients are getting collected and sent for our testing.

So we definitely have a skewed perspective of how these tests are performing in that particular setting, and I think, given the goals of what we want here for

hepatitis-C screening, we should not discount this disconnect.

DR. GITTERMAN: I could absolutely not agree more. I would say, though, as part of the approval process, PMAs are approved; 510Ks are cleared. It took me three years of working here to understand that. In the PMA process, a lot of negative samples are being tested. And again, PPV and MPV would probably be the ones -- with the performance characteristics we have -- that would probably be most effective. The less your prior probability, of course, and the lower your prevalence, the lower your PPV is going to be.

But right now we feel, in the environment, these are very good tests. And again, under the circumstances now where the gentleman sitting next to me has recommended everybody from 1965 be tested, one could say a lot of those patients are symptomatic. I have to say, most patients with HCV early on, a large number -- that's the trouble, getting acute patients -- are either very non-specific or completely asymptomatic.

Your point is absolutely correct that, as you go to less and less prevalent populations, sensitivity and specificity are key. But again -- and I certainly welcome Dr. Dodd's or Dr. Luce's comments -- since this is a

situation where I would suggest as a practicing physician that specificity is not as critical as sensitivity, we might tolerate more false positives. For HIV one could argue the same but there is a much greater societal impact. And other tests, you sort of have to argue, telling a married couple that he's positive for herpes doesn't go too well in a lot of cases.

But this is one I think we could reasonably argue that false positives are less significant than false negatives. Ines, would you like to comment?

DR. MILLER: With regard to new tests coming to the FDA that, under Class II, would be compared to a predicate device, it would still have the intended use only for testing symptomatic patients. Is that correct?

DR. SCHLOTTMANN: Yes. A significantly different intended use would not be able to be compared to a predicate. So, as soon as the intended use is different the route for submission may be different, and there may be either a Class III or *de novo*.

DR. GARCIA: It would be an at-risk population such as with the CDC risk factors that are outlined in the website are also a symptomatic population. Those are the ones that are currently being evaluated for all our tests.

DR. MILLER: So that includes everyone born from 1945 to 1965?

DR. GARCIA: Yes, because they are considered at risk.

DR. DODD: I just have a question that I would like some input on. I am not sure from whom. One of the advantages of having such high performance is you can get by with some pretty small sample sizes to get these bounds. I just want to ask if you are comfortable getting a submission on the order of 50 positives and 50 negatives, or do we want to have --

DR. GITTERMAN: No. Given the diversity of the populations we want studied, the different groups, symptomatic, not symptomatic, et cetera, it would be exceptionally likely. I don’t want to proffer very high numbers which will make Mr. Spring keel over, but the fact is no, you are not going to get by with 50 because there are enough subgroups to say the use may be wide.

I also want to point out that even though we certainly want capacity that gets the very high predicate, in some cases -- and again, Dr. Schlottmann could consider -- there always is some type of discordant analysis. Even with a high-performing test you can get slippery slope. It’s not that hard, especially because it’s so high

performance. And it is not, in every case, solely that we just say how did it compare to this. When sponsors miss, we don't include it in the actual results because that is not the *a priori* protocol, to find definition, but of course, if somebody could go back and do sequencing using another test and show in fact it was positive, we would consider that as a discordant, as a positive result. We are not foolish.

So, even though the predicate is very important, we certainly have controls against -- to lose the fact that predicates can slip as well. Having a high performance predicate doesn't always eliminate the problem.

DR. SCHLOTTMANN: As Dr. Gitterman pointed out, this would be a discordant analysis, so we would include such information in the results section but usually as a footnote to performance tables. We would not -- It's the manufacturer's responsibility to choose a predicate that works for them, and if they have an increased level of discordant results, they will be displayed as such in the results section. They can perform an additional analysis and we will include the information on it, but the performance for that test will be calculated on the actual results in comparison to whatever comparator they choose.

MR. SPRING: Let me just add a point of clarification, and FDA, please comment. A predicate is not always a comparator. A predicate may actually be the mere fact that there is a test with a similar intended use on the market; therefore, you can follow the 510K pathway, but your comparator may be a completely different test. That is why we try to draw the distinction between a predicate device, from a pure paperwork exercise, to an appropriate comparator which is what you are testing against.

DR. GITTERMAN: I could not agree more that the goal is to get an acceptable comparator. I'm sure Dr. Dodd could lecture us forever that if you have a test that's 99 percent performance and that's your comparator, it's going to be very difficult, even if your new test is 100 percent accurate, to in fact achieve that.

I don't need to explain it; she can do better. But the fact is when you get that high it's very difficult. And Brad is completely correct. It does not necessarily have to be a predicate device. It has to be an acceptable comparator.

DR. DODD: You said that a sample size of 50 positives would not be sufficient, and I agree. But you followed that with there are enough subpopulations that you want to explore. So, when I read the document with the

special controls that are proposed, it was not totally clear to me what the subpopulations are and what you would require. Is that something that's worth discussing with this group, or did I miss it as a statistician not really fully understanding that?

DR. GITTERMAN: No, no. I take full blame for that. When we were talking about writing this manuscript I said let's not get too much into the weeds.

Of course, as you recognize, when we're looking at subpopulations we cannot establish lower bounds for each subpopulation. That was the same issue with the first genotypes. However, since the overall performance is so high, no subpopulation can perform very badly, so we would expect overall very good performance, and we expect point estimates that are virtually identical within the subgroups.

Your specific question is what subgroup we would like and we certainly defer it to Silke or Dr. Garcia.

DR. DODD: I guess the reason to push this a little bit is because I'm assuming you will be getting submissions with smaller sample sizes, and, therefore, you may just simply not capture enough or even any from a specific subpopulation. So it's a question of whether you

want to have some more targeted sampling to get enough in certain subpopulations.

Maybe in the past you captured them because you had large sample sizes and now you will never know that this test doesn't work in that particular subgroup.

DR. GITTERMAN: Absolutely. Again, there are panels out there that there are four levels of evidence. You could use retrospective samples, which is why having banks is invaluable. Sometimes companies just miss it. As Dr. Schlottmann put in her slides, if you don't get a certain level with a compromised host we just say it is not indicated for that use.

I certainly think we hear loud and clear that pediatrics is a very important subpopulation. People around the table can say anything they want. This is a public hearing, it's an open forum. Silke, would you wish to comment on some of the subpopulations?

DR. SCHLOTTMANN: In general, as you guys may have seen from the labeling of our products, we are asking that all the most prevalent genotypes are included in the clinical study. Recently what we have done is we have asked that the distribution in the U.S. is reflected in the sample cohort that's tested.

Now, that being said, I appreciate the concern that is behind this and also the specific proposals, but I want to emphasize that the more specific we are in the language in the special controls, the less flexibility we have. In order to work with manufacturers on certain misdistributions maybe in their sample cohort, we want to leave some wiggle room in the language in order to allow that flexibility for us to work with them to get, of course, an acceptable and high performance but with what they can do.

DR. DODD: I am assuming you can construct the language to be general enough that you are going to expect some minimum number in some subpopulations and leave you the flexibility to negotiate whatever that should be with specific companies.

DR. SCHERF: I would like to have a follow-up question. What I think I am hearing from your concern is that it’s very clear you want to have a certain number of positive samples being evaluated during the process of the submission, which we total agree. We thought -- correct me if I’m wrong -- with defining the point estimate and statically the lower bound, you by definition already defined the certain number.

But what I am trying to understand is now do you think there is something else that you see a risk that we should consider? Because, really, the point estimate and the lower bound gives you a number, and normally that is also our argument, that if you reach that number why do you need more. I sense that you have something in mind that maybe we don't understand yet and maybe you can describe it to us.

DR. DODD: Really, I am thinking about a problem that can be best characterized as spectrum bias, from a diagnostic accuracy perspective. If you are only getting -- this is not what I'm sensing here, but -- if you are only gettingthose with a really high viral load in your sample, of course, you are going to get really high performance.

I guess I'm trying to push towards what is the stress task of these new tests, and where is this most likely not to perform well. It's important to consider when you're going to be moving to a study design that will be reducing the overall sample size because you are less likely to just pick those up unless you ask for it.

DR. GITTERMAN: A couple of things. We have quite a bit of good data now from well performing studies to show the expected distribution. We really have a very good sense of how many, in a distributed population at supposedly

different times after disease onset, what the viral load, what the distribution of expected results in a population like that should look like. So I think we have a pretty good sense on the low end and the high end.

Also -- and this is sort of difficult to communicate -- there is a lot of biological plausibility. We were dinged, so to speak -- we have guidance, very specific when you talk about subpopulations, that addresses age, race and ethnicity, where we are called to include so many specimens. Now, you hate to say it, but if you want the sponsor to get positive prospective specimens, it’s not random. You’re not going to go to the middle of Iowa and get people, and we were dinged to say, well, there was quite a distribution of a certain ethnicity in the positive samples for your hepatitis-C study and where you studied it. And we just said, well, this is the Willy Sutton theory. You’re not going to get positives or you’re going to get a lot of negatives.

Again, Ines could talk about the serology. But for viral load and detection of RNA, nothing has been suggested that there is ethnicity-specific or race-specific. There may be different distributions of analyte, et cetera, epidemiological difference, but for detection we

have not found that there has been any difference that we could say that would change. But your point is very good.

I also think, too, one of the reasons that it's being proposed for reclassification is that we have so much data on there and we can look at this because some of the tests have been very well performing.

Another thing I could say is sponsors are required to do reproducibility studies, a lot of analytical studies which give you quite a good bit of device performance, not prospectively studied, not across a lot of different populations, but you do get a very good sense of how the device performs analytically. A lot of the cross-contamination tests, all the LoD tests, all the tests against different genotypes -- that gives you a lot of information. But again, that is not answering your question because your question is against a diverse population with different degrees of prevalence and different characteristics.

DR. CALIENDO: Roger is going to have the last comment and then we're going to go to the public comment, then we will come back for more discussion.

DR. LEWIS: If I may, I think one of us is missing Dr. Dodd's point so we're going to find out whether it's me. There are sources of variability in test performance

and they can come from multiple different places. One source of variability is the difference between tests you have seen versus the tests you're going to see in the future, and the risk associated with a reduction in the criteria for approval is that the test you see in the future is actually not going to perform as well as the test that you have grown to be comfortable with and fond of.

The sources of variability can be test level, they can be operator, they can be sample processing. Those you probably are going to get quite a bit of information about, and we probably understand those pretty well.

Then there's the patient population functions, so, spectrum bias, the distribution of the thing you're detecting in the population, the presence of other infections that have some sort of blocking effect. I'm just making stuff up because this is the unknown unknowns. And the heterogeneity by sort of the traditional things we look at, race, ethnicity and age. We only use those because those are easy to come up with, not because they are necessarily the greatest way of distinguishing populations in which there's likely to be a difference in test performance.

The way I interpreted Dr. Dodd's comment was that she was asking the agency to think very carefully about the

subpopulations you should be thinking of that are likely to differ in things that will affect test performance, not just check off either the ones that are required by law or the ones that are convenient.

I think what we are looking for are two things. One, some careful thought about what are the subpopulations for which the test performance might be worse, and we would like to know that before we approve the test. Then, a willingness to actually write down what the performance is that you would like by those subpopulations.

For example, let’s suppose you are interested in the pediatric population -- I’m purposely picking something about which I know nothing so it frees me up to make up a story -- and the distribution of the RNA load was quite different in that population, and you’re looking at a test in which it’s getting both a diagnostic qualitative label and a quantitative one.

I would want you to be willing to write down in slide 18 what you would want the sensitivity and specificity to be in that subpopulation with a lower bound, and you may choose to have a lower bound that’s different than the lower bound you would use for the population in which you set these standards, but I would want you to be willing to write it down.

To be honest with you, the argument that you want to have some sort of mixed rate -- that just doesn't hold any water with me. I think you want to think about it carefully and be willing to write down what should be the lower bound for performance that you are willing to expect in a screening population or in a symptomatic or at-risk population or in a pediatric population or, ultimately, in a test that's intended for a point-of-care environment, and those can all be different but you should write it down.

DR. GITTERMAN: A couple of things. One is your points are very well taken. Under the current approach to clinical trials for what we would expect, you are required to have three different sites, and we ask for them to be geographically distributed and in different populations, and we have rejected applications. We had one application which was completely studied in Salt Lake City, and even though we had warned them they said, no, it's very diverse. And it had absolutely no diversity so we had to reject the application until, ironically, they had to go to Hopkins to get more diversity. That would be number one.

Number two is your points are very well taken. On one hand, we certainly know the number of pediatric samples is going to be very small. We would likely expect a similar point estimate -- lower bounds are always going to vary. If

we could identify every subpopulation and the statistical rigor we want around each one, we would probably be awake until 2025. It's very difficult. And I have to say, for some of these tests, we haven't identified a population where we would expect necessarily different performance. In an immunocompromised patient perhaps we might expect some difference in serology but we might not expect any difference in viral load.

I certainly would welcome, given all the experts we have around the table, Dr. Thomas and certainly if Dr. Kim and Dr. Kamili want to comment, what those populations are. But I would say that trying to ascertain on a benefit-risk basis specific boundaries for every subpopulation I think might be a mistake *a priori*.

DR. LEWIS: That's why that is not what I was suggesting. I did not say that I wanted you to have the perfect be the enemy of better than what you are doing. What I'm saying is I would like the agency, with the expertise that you have available to you either internally or externally, to think carefully about what the finite number of subpopulations is in which you might be worried about heterogeneous test performance. Pediatrics I think is an obvious one. The immunocompromised is an obvious one. Probably age is another obvious one.

And come up with that and be willing to write down what you think are the appropriate standard performance criteria within each of those so that the subpopulation representation and the data that are submitted to you in a 510K application allow you to make some assessment about whether the performance you asked for is actually demonstrated by the data presented to you.

DR. GITTERMAN: I think that is very fair, and my apologies for misinterpreting. We do that regularly. Tests like immunological-based tests that we all use and have a lot of variation between subpopulations for a lot of reasons, and it is well recognized. And we certainly would welcome any committee recommendations regarding that.

Certainly, if Dr. Kamili or Dr. Kim have a comment they are welcome to make it.

Agenda Item: Open Public Hearing

DR. CALIENDO: Let’s move on to the open public. We are at 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 is conducted on a particular matter of general applicability. Welcome to the open public hearing session. Please state your name and 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 the advisory committee meetings, FDA believes that it is important to understand the context of an individual's presentation. For this reason, 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 may be affected by the topic of this meeting.

If you do not have any such interest, FDA encourages you to state that for the record. If you choose not to address this issue of financial, personal or professional relationships at the beginning of your statement it will not preclude you from speaking and you may still give your comments.

For the record, we have received one formal request to speak at today's meeting. Each speaker will be given 10 minutes to address the panel. We ask that you speak clearly to allow the transcriptionist to provide an

accurate transcription of this meeting. The panel appreciates that each speaker remain cognizant of their speaking time.

Our first speaker today is Dr. Shiffman from Roche.

DR. SHIFFMAN: Thank you very much, Madame Chairman, and members of the committee. Thank you for allowing me to speak. I am going to address assessing HCV RNA from a clinical perspective. These are my disclosures. I have worked with Roche Molecular Systems in the past. I was the principal investigator for their development of the Roche cobas assay many years ago and am here as a consultant on their behalf.

However, I am a clinical hepatologist and have a large hepatology practice in central Virginia. I take care of many, many patients with hepatitis-C, as I have had throughout my career, and I am going to give you a medical perspective on the use of diagnostic testing.

Chronic HCV is still an important disease, has a prevalence as you know of four to five million persons, and treatment has been available since 2000, but this treatment has not been very good. It has been very toxic -- that’s peginterferon and ribavirin. It has side effects which

limit its use in many populations, and it has a low cure rate.

Oral direct-acting antiviral agents first became available in 2014 and have a very high cure rate, almost everybody is cured. They have virtually no side effects during treatment, but this does not reduce the need for reliable HCV RNA testing, and that is an important point.

This lists the different oral antiviral agents that are currently clinically available and approved by the agency for the treatment of hepatitis-C. The one that is greyed out is specifically for retreatment of patients who have failed most of the other drugs. You can see they all have incredibly high sustained virologic response rates, in the 97 percent to 99 percent range.

What I want to show you here is what has happened to a number of patients with hepatitis-C who were treated since we moved into the direct-acting antiviral era. During the peginterferon era, which lasted 14 years, very, very few patients were treated, and you can see that even a smaller number of patients achieved a sustained virologic response. However, in just four years we have doubled the number of patients who have been treated for hepatitis-C and virtually all of them have been cured, with a very small uncure rate or relapse rate of less than 3 percent.

As a result, the number of patients treated annually is expected to increase year after year, and we expect non-specialists who do not know a lot about the diagnostic accuracy of these assays and the intricacies of treating hepatitis-C to enter the treatment field as novices in treatment, and they have to rely on and be absolutely sure that diagnostics are correct.

The role of HCV RNA testing is to confirm the infection, to determine the duration of treatment, particularly with Sofosbuvir-Ledipasvir, to confirm that the patient is then being cured of their hepatitis-C infection, and the issues of concern for providers, especially novices, are the false negative and false positive rates of any new assays that come on the market with less rigid requirements.

You have seen a similar slide by one of the presenters. We screen with anti-HCV. We then confirm with RNA. We must be certain that a negative result is reliable, and a false negative result leads to a patient who really has hepatitis-C not being treated and going on to develop worsening disease with their infection.

I want to give you three case examples during the course of my talk. This is the first one that points out

what happens when you have a negative C. These are all real patients from my practice.

This is a 52-year old African-American female, normal liver enzymes, normal liver function. She had a positive anti-HCV test during birth cohort screening, but HCV RNA was undetectable by her primary care physician. However, she had a liver ultrasound that suggests she had chronic liver disease and they thought it was fatty liver, so she was sent to me actually for fatty liver disease. But she had strong risk factors for hepatitis-C of intravenous drug use, so, just to be sure, we retested her for HCV RNA and she did have a low level positive infection and then went on to treatment.

This shows the importance of properly assaying the level of HCV RNA. With the Ledipsasvir-Sofosbuvir combination, if the level of HCV RNA is less than 6 million units and the patient is non-cirrhotic in treatment IE, we can treat for as little as eight weeks and achieve a sustained virologic response rate that is equal to the 12-week duration of therapy.

However, if the HCV RNA is greater than 6 million units, there is a much higher relapse rate, as you can see in the inner bar, tenfold increase in relapse, and as a result, you cannot reduce the duration of HCR treatment

from 12 to 8 weeks; otherwise, you are going to get a much higher risk of relapse. So, knowing the virus level and knowing that that assay is accurate in determining the virus level is very important.

This is a case where a patient relapsed with eight weeks of treatment. A 62-year old Caucasian female, liver enzymes are elevated as you can see, platelet count is kind of borderline -- not in the cirrhotic range of under 150 but very close -- and ultrasound shows chronic liver disease and a fiboscan shows a lot of scarring but not yet cirrhosis. Everything is borderline, and the HCV RNA was just under 6 million units, and as a result, the insurance carrier mandated that we treat for eight weeks of therapy, but the patient then went on to relapse.

So, if this virus level had been just over 6 million units, then the patient would have gotten 12 weeks of therapy. But again, it just points out the importance of being very precise in that HCV RNA measurement.

We used to monitor HCV RNA very frequently during the course of therapy, but now that we have such good treatments where almost everybody is cured, many societies are recommending that we reduce the frequency of HCV RNA testing. We now do a baseline during treatment, recommend no testing, but the reality is that HCV RNA is tested by

many at one month and at the end of treatment. After treatment, it’s recommended just a single test at three months, but the reality is that a lot of physicians will test at one and three months. When all of a sudden you have a lot of novices getting into the market and they test less frequently, it’s even more important that that HCV RNA test has been verified and we know that it’s highly reliable.

That leads me to my third case, a 68-year old Caucasian female -- this is from our practice -- who had elevated liver enzymes, genotype 1, baseline HCV RNA about 8 million units. The patient was treated for 12 weeks with Ledipsasvir-Sofosbuvir, and 12 weeks after treatment HCV RNA was undetectable. No liver enzymes were obtained, and the patient two years later was found to have elevated liver enzymes.

This previous treatment was by another gastroenterologist. The patient was then referred to us -- excuse me. The liver enzymes were elevated and then the patient was retested for HCV RNA and it was positive but now had genotype 2. So this patient probably had a mixed infection with genotype 1 and 2 and, because there was only a single HCV RNA test, was negative and didn’t pick up on the fact that the patient relapsed with the other genotype.

So these are interesting cases, but they do exist. I am a hepatologist. I only take care of people with liver disease. I get referred a lot of patients who have these weird or non-standard responses. But there are many of them out there and we have to be sure that our test is reliable enough to pick up all these patients.

In summary, the vast majority of patients out there with hepatitis-C are still going to require treatment. Treatment is highly effective and almost everybody is cured. Treatment can be readily accomplished by non-specialists and I am an advocate of that; however, non-specialists may not recognize the occasional patient with discordant HCV RNA results, and, therefore, HCV RNA assays need to remain as perfect and as sensitive as they can possibly be. Thanks very much.

DR. CALIENDO: Thank you. Does anyone have any questions for Dr. Shiffman?

DR. WARD: Just a small point on your talk but a big point around the country is that the number of people being treated for hep-C is actually dropping because testing has not kept pace, and you have the warehouse effect, which I am sure you are very familiar with. So, one of the issues here is how do we make testing more readily available and then get those people into care so that the

testing does indeed remain at a level that we can achieve the elimination goals that we have set for the country.

DR. CALIENDO: Thanks. Does anybody else in attendance want to address the committee? Now would be your opportunity.

(No response)

DR. CALIENDO: Okay. I think what we are going to do is break for 15 minutes, and then when we come back we are going to go around and continue our discussion with the goal of everybody addressing the question that the FDA has posed to us, and if you have any specific thoughts on special controls that would be a good time to express them.

Committee members, please do not discuss the meeting topic while we are on break amongst yourselves or with any member of the audience. We will reconvene in this room at three minutes after 3:00. Thank you.

(Short break)

Agenda Item: Questions to the Panel and Deliberations

DR. CALIENDO: At this point I want to open the floor to the experts around the table to begin deliberating on any issues that you may have with any data that you have heard today. At this time, we need to focus our discussion on the FDA question, and I will read that question for you.

Do panel members believe that the risks associated with the following HCV tests can be mitigated through special controls? They have broken this down into antibody tests, qualitative and quantitative RNA tests and/or genotyping tests.

I want to remind the panel that this is a deliberation period among the panel members only. Our task at hand is to answer the FDA's question based on the data and the panel packets and what we have heard today and the expertise around the table. What I would like each panel member to do is identify themselves again when they speak. We will have a discussion for a while and then we will go around and each panel member will be able to express their opinion.

This is not a formal vote; it is just your opinion. And if there are any specific special controls that you want to comment on or think should be added in addition to what the FDA has presented, now is your time to do that.

I'm having a hard time seeing everybody's hand, so just use your card and put it upright and then I'll know that you want to speak. Thanks.

DR. KIMBERLIN: David Kimberlin. Just a clarification of what the process downstream of this would

be. Is this going to come back to us for a vote, or is this our only chance to weigh in?

DR. CALIENDO: This is your only chance to weigh in. They will not have a formal vote on this. Questions? Thoughts?

DR. LEWIS: A question for the Chair. If we wanted to move to just giving our opinion, is that acceptable or does that preempt the process?

DR. CALIENDO: As long as no one else has any other comments. We have had a lot of discussion today. I don't want to cut it off. We can easily go to our comments if people are comfortable with that. Do you have any other information that you want? Questions, discussion?

What I need to do is summarize your brilliant thoughts. When we go around, be just as clear as you can be because I have to pull it all together for the FDA so that I have a summary of what the general thoughts are of the group. I just want to make sure that you have adequate time for discussion.

MR. REES: In the Executive Summary -- I think we have referenced it a couple of times but not much -- there is a whole section on proposed special controls. All HCV tests, quantitative, qualitative, qualitative HCV RNA. Is that what we're addressing? Because that is definitely not

what was in the slide earlier. I am not sure what that proposed special controls in the Executive Summary is referencing.

DR. GITTERMAN: I am surprised there's a discrepancy, to be honest.

MR. REES: This is much more detailed. That's what I mean. So we are looking at these details?

DR. GITTERMAN: Yes, sir.

DR. DE VAN: Michael DeVan. I apologize; I missed yesterday. Is it industry's opinion and the agency's opinion that industry does not move forward with creating the device that doesn't exist that we've been talking about if we do not reclassify?

DR. GITTERMAN: I don't think I can comment on it. I don't think it's fair for the FDA to comment, but I will defer to Mr. Spring for an industry perspective.

MR. SPRING: Could you repeat the question?

DR. DE VAN: I am just wondering is it the opinion of industry that they will not move forward with creating point-of-care type devices without the reclassification?

MR. SPRING: Yes. I can't speak for all of the industry, but I think the number of tests coming to market would be far lower without reclassification. A lot of startup companies do rely, say, for example, on venture

capital funding or other funding sources. They will look at the environment and maybe the risk of not coming to market before they make decisions on whether to offer up that funding. I think when you see down-classification the risk gets lowered, of success, and that opens up more funding.

DR. DE VAN: This is a follow-up for the agency. We are being asked to say do we feel that risks could be mitigated through special controls but we haven't elucidated every possible special control at this time. It is fair to say that if we feel that special controls could exist for this process, then the answer is yes. Is that fair to say?

DR. GITTERMAN: That is a difficult question to answer. If you're going to say does the agency have an opinion, we could say that we have a lot of experience. Dr. Lewis asked before what our experience had been. We wrote down reasonably detailed special controls. I also have to be careful to say that this is a regulatory agency and the special controls we propose go through counsel review to see what is consistent, because sometimes we could propose the moon and it just may not be legal.

But the assumption is that we would be able to generate a set of special controls. But we certainly welcome -- and again, I am tremendously grateful.

Certainly, the point about pediatrics was very important. And as we go around the table, if there are special controls that you think we should focus on that will help ensure safety and efficacy, we would much appreciate this being brought to our attention.

But I do think we have -- and I should credit, of course, Dr. Schlottmann and Dr. Garcia -- a credible first pass at what we would look at for special controls.

I would also suggest, too, a lot of it is based on what we did previously for CMV which was done with the help of not this half of the table but some of the people on that half of the table about a year and a half ago.

DR. CALIENDO: Patricia, who is on the phone, would like to ask a question.

MS. LUPOLE: It is actually maybe more of a comment. I think this is a great opportunity to reduce costs for advocates who go out actively seeking patients or populations to test. The only thing that concerns me is now that it’s leaving regulation and entering a manufacturing guideline, so to say, the ability for the manufacturers to reuse the device for another purpose, especially on the antibody testing -- I agree with Dr. Ward 100 percent that we may find these patients but we lose them to getting them

back in and finding out how to best treat them and serve them.

So I would caution that the FDA make sure that the special additions do somehow hold control over the purposing of the exact device. That's about it. It's a wonderful group, very informative. Thank you.

DR. DODD: I hope this gets a quick answer from the FDA, because I am still trying to get my head around the difference between a Class II and Class III and the implications.

On slide 9 from Dr. Garcia's talk it says that for a Class III device there's an annual report required but not required for a Class II. Is there anything in that annual report that one would want with a reclassification like this, or is all of the expected reporting like the MDRs, et cetera, would that be coming in anyway? Is it an easy yes, there's nothing we would be missing?

DR. GITTERMAN: Nothing is easy in life. In fact, under a 5.10K one can require annual reporting. Right now, our thinking is the ADRs, adverse events, would not affect it at all under an annual report.

Now, for specific reasons, if we felt there was a valuable reason for an annual report we might propose one in a special control. Certainly, I know CBER has thought

about that in the HIV arena. Right now we have not proposed that, but it could be if there were a good rationale for it and we thought it could affect either the benefit-risk or the safety and effectiveness of the device. But EDRs *per se* would not be affected under our present system.

Now, if we wanted to ask for another special control, it would be worthwhile to have the manufacturer summarize them and present certain things that aren't done in a certain way, then we could certainly ask for it. It's a complicated answer.

DR. ADEYEMI: That was kind of a follow-up to that question regarding it's good to know that the analytical controls and all of that are still the same.

But regarding the reporting post-approval, the question was is there ever a time where there was a hybrid where at least for the first five or three years after approval there was annual reporting, things like that. I didn't know if there were absolute, like the 510, definitely new required reporting or, with new devices, new things that are hitting the population, if there was ever any kind of post-marketing or post-approval reporting that would be required.

DR. GITTERMAN: Perhaps I can address it generally. Ines, you had looked into all the ADRs for the

devices that have been cleared, or Silke did. But general reporting is required. This is all passive reporting, as you might expect. There is not any type of active surveillance.

I would say, honestly, with recalls or evidence of some product quality issue or something, that usually comes to us as a case report or a single report which then we investigate. We look at every report they have submitted, and based on that, that very commonly is a key to what has occurred, because -- same for drugs -- it's a fraction of the adverse events or malfunctions of devices that actually get reported to FDA *per se*.

For the existing devices, in preparation for this meeting Dr. Schlottmann actually looked at a review of how many recalls there have been for the existing devices. Do you want to comment, Silke?

DR. SCHLOTTMANN: The result of the analysis is in the Executive Summary, way at the end. Considering how long some of these devices are out on the market, there were astonishingly few adverse event reports associated with these devices.

I think one of the major challenges is to get the end user to report, so it's a little hard to assess in what way the reports that are available are reflecting true

false results. A lot of the reports that are in there, from what I have seen, you couldn't make a definitive statement on whether this was really a false result -- things like, well, I got a negative result with this test; I got a positive result with that test. But we don't know which test is correct. A lot of time, further analysis is missing.

So, my general feel from what I have seen in the adverse events reported is it's fairly few for these devices, so they are really high performing. That is all I can say. And most of the events that were reported I think were related to false negative results, if I remember correctly.

DR. CALIENDO: Having read all of this, that was kind of the impression that I walked away with. We have a lot of years' experience with these assays and very few adverse events. We have to think about, if we're going to say, yes, we think lowering the classification is a great idea but then we institute a lot of what makes it a PMA, we're not really helping the manufacturers get to where they need to go.

I think one of the reasons we are here today and one of the reasons we're having this discussion is because

we have so much experience with these tests and they have performed at such a high level for so long.

My question to you is -- and it’s exactly what was just answered -- in all these years of all these annual reports, have you found anything in there that makes you nervous, that makes you uncomfortable that we are having this conversation today?

DR. SCHLOTTMANN: No.

DR. SCHERF: I just want to make one additional comment. When the conversation initially started about the special controls, that actually very detailed list in the additional documents, I think what we would like to share with you during the deliberation now is we are not expecting that you now come to us with defined special controls. That is not your business; you’re not really used to this kind of wording, and we are not expecting that.

I think what we would like to see is whether the ones that we already have shared with you, whether they make sense. But if you are in knowledge of additional risks, if you could during your deliberations share these with us, because then we can take the notes and later on define and write the special controls that we believe could address some of these risks.

This is just to Dr. DeVan's comment on how can you help us get this information in our hands, so, really, don't try to define the special controls but share with us the risks.

DR. THOMAS: In that regard, a couple of comments. One is that with the molecular tests, to my knowledge, the only performance issue that I have ever seen in the literature or in experience is with genotype, with template. That was already reflected and I just would underscore that. Anything new needs to be able to detect the range of templates -- it is possible -- which has fortunately not been a problem.

With antibodies, on the other hand, there is a low specificity of the existing tests in, for example, persons from Sub-Saharan Africa. So the 98 percent that's on that slide that we all talk about, that is generally what happens but not in certain settings. So that and any other population where antibody is an issue -- so, HIV, renal dialysis, pregnancy -- those are the range of situations and it's just logical because it's an antibody test. Whenever there's a precedent for a difference in antibody production I think those should be enriched in the experience.

The genotyping, I would say don't try to go near mixed genotype detection. You will never leave that quagmire. But like was said earlier, the ones and twos and threes are where you need -- where a new test should be sufficient.

And a final comment, back to the molecular test. I believe that the issue with the accuracy of molecular tests in infancy has to do with the lack of an antibody test to resolve -- to differentiate between a false positive RNA and a spontaneous clearance of infection, and it' probably true that infants spontaneously clear more than adults. So it has been vexing to look at the literature and to understand what is a positive test in a four-month old, a positive nucleic acid test.

But I don't think there is any evidence that those are biologically more complicated to do in plasma from a four-month old, so I don't think the age of the plasma affects the accuracy of the test. I think it has been more complicated to interpret those, and that's what has led to concerns and the more conservative guidelines calling for 18-month antibody detection as sort of a -- well, let's just recommend that because we can be sure what we're getting -- kind of practical form of advice.

DR. ORTEL: Tom Ortel. We have had discussions about limitations from limited numbers of patient populations that could be studied, discussions about limitations on viral genotypes, et cetera. I do like what's in the Executive Summary because it is definitely much more detailed than anything we saw anywhere else.

But one of the things it does not necessarily say is I don't think we could ever predict all of the variables that may come up, but are you collecting sufficient data on the data that you're getting that you would be able to go back and figure out if a test had passed, but you didn't have any of that serotype in there, or you didn't have any of that cohort in there. Is there sufficient characterization of the data being required that gets turned in?

DR. GITTERMAN: That is a really good question. Certainly for the prospective studies a lot of things can be identified. For retrospective samples sometimes you don't have all the information you would prefer. And I suspect as you get to small -- you know, what is a true subpopulation? It was not that many years ago that studies for drugs always considered -- no one believed that gender was a potential variable for any differences between.

So, the data is the data. Gross sub-populations we could. But since performance overall is so high it would be very, very unlikely one is going to find a subpopulation with a difference, but true, within the limits of the data that's collected we could always go back to see what numbers of those people that had been tested were studied in that specific group.

Again, if there are specific groups, biologically, it's hard to think of groups that might differ. They might differ in quantitation conceivably, detecting versus not detecting RNA, and for the antibody test there may be a different result. But more commonly, as Dr. Thomas just said, it's going to be a false positive. So the answer is usually we have what we have.

I could tell you -- and I don't mean this with a smile on my face -- it's very expensive and difficult for companies to collect a lot of data, and that is an enormous push-back we get. Like, why do you need this data. And our less burdensome provisions we often have to compromise to see what's reasonable and what is not reasonable.

Mr. Spring might want to comment. That's a big expense to have somebody come in and say do you want to participate in the study of an informed consent, and now you're asking them a lot of questions which you are

unlikely in the long run to deal with. I wish I had a better answer but I don't.

I can make a couple of comments. If I could just go back to your question, I think you're a little late to the table. All the genotype devices will have interference studies where they mix different genotypes -- and please feel free to correct me, Zilke -- where they mix these and look at performance and analytical studies, so it is well looked at, at least pre-clinically in that case.

I don't have my hands around this too well, but the future with the electronic health records actually has a lot of promise in terms of -- like in the example that Dr. Thomas said, if you could go back and look at serological tests -- and of course positive ones will have a confirmatory test with them -- and say look, what populations are having far less than expected positivity for the confirmatory test, that would suggest at some point that some populations have more false positives than others.

So I think the future may offer us more targeted post-marketing surveillance than is available now, but I don't think we are there yet. There's a lot of FDA activity looking at real-world evidence and what we call semantic inter-operability, but I think that's a few years away yet.

But it is a very good question. Are you a lumper or are you a splitter. It's a practical and an important question. Certainly if people around the table have comments we welcome them.

DR. DODD: Again, Dr. Ortel's comment raised another question about the shift from a Class III to a Class II. That is, does the FDA even get the data? Because it says on slide 9 that similar studies are conducted but not included in the FDA's submission.

DR. GITTERMAN: Yes.

DR. DODD: So you still get the data --

DR. GITTERMAN: We will have the line data, correct.

DR. DODD: Okay, great.

DR. KIMBERLIN: The comment made about how these tests perform in young children, infants and even neonates is unanswered right now. As we have discussed and as I have been hearing, and very reassuringly hearing, in the conversation, the agency is committed to trying to encourage the generation of those data, and that is reassuring to me.

The kinetics could be quite different in terms of when babies turn positive. HIV would be a good analogy. If you test early on, very early on, just a matter of days,

you are only going to see 40 percent or so positive and, by two or three months or four months, higher. We may find similar things with hep-C. We need to know it.

I am personally comfortable with the move from a Class III to a Class II. I was a little unnerved by the precision of some of the statements with the slides, but then upon questioning see some flexibility that was not part of those statements. I certainly understand flexibility as being needed from a regulatory standpoint and would not stand in the way of that.

I guess, ironically, I am reassured we're not going to be asked to vote, because if we were asked to vote I would want to know exactly what the language was that I was voting on. But if it's more of a general 5,000-foot view, I don't see much difference in terms of risks and benefits whether it's Class III or Class II, and I see opportunity as a Class II to get more products on the market, which is what we need, and to have more opportunities for investigation in the population that I care most about.

MR. SPRING: This is a follow-up to Dr. Caliendo's question around what are you seeing in the annual reports or other submissions that may cause concern, specifically on the special controls request or at least the total life

cycle piece around having to submit release criteria and, I believe, changes in shelf life. Let's say you start off with six months, then you go to nine, 12, whatever and you would be submitting that. That is a little different from what I have experienced, too, in down-classifications.

Is there a rationale for asking for that now? Is there a concern that you have seen which would require that type of information to be submitted?

DR. GITTERMAN: I would suggest that in a lot of internal discussion, of course -- the discussion has been internal to date -- for this use -- and I would repeat the statement -- HCV is felt to be a public health concern. I don't want to cite experiences we have had in the past, but there's a concern that requiring that would be important -- or we wouldn't have proposed it otherwise -- for maintaining safety and effectiveness across the total product life cycle.

I do think, though, there is reasonable and unreasonable. And I think, if this goes forth -- the nature of what those submissions are -- I think there is clearly variability. We have presented it as a whole, but our goal would be to implement it in the least burdensome way.

But I think from our experience -- and publicly we cannot discuss it -- that gives the avenue sometimes for

-- and again, I would never ever accuse any specific company of anything because I know every company up front is doing the best they can, but sometimes there may be fair disagreement on what is a significant change and not. By defining it in the special controls, if you look at the Mod guidance, it does mean the company has to address it, but I would hope we can do it in a way that is least burdensome.

Again, it is beyond the scope of this committee, but there are different ways that we could, I would hope, not hold up the company and the implementation of changes in that regard. But it gives us the power to make sure something we think might be a big mistake is not implemented in that way, and we could decide that it's unnecessary at a certain point as well.

MR. SPRING: Just a quick follow-up. We talk a lot about new entrants to the market and how down-classification would help that. I think we have also discussed in the past that modifying tests and proving them I think is also potentially a challenge in a Class III environment because of the -- most of the post-market submissions. So I would see that as another advantage, that it would incentivize companies to do more improvement to their product.

DR. CALIENDO: I think that's a very important point that has come up with other pathogens, the reluctance to come back through because of what's involved. I think that is a very fair and important point for the group to understand.

Any other comments?

We will go around one at a time, and let the FDA know your thoughts on going from Class III to Class II. Then, if there are any additional risks that we -- We have talked about some interesting things today and I have some notes here on pediatrics as an important population and a few other things. If there is anything else that you're concerned about, now would be the time to bring it up.

MR. SPRING: This is Brad Spring. I'll be brief. I do support down-classification. I appreciate, by the way, the FDA's thoroughness in the pre-read material. It's too bad we couldn't talk about HIV as well, but I didn't personally see significant risk in this down-classification.

DR. STAPLETON: I too support the down-classification, and you mentioned the pediatric controls. I guess the other controls like, clearly, the immune-suppressed. And I think it is standard for FDA to require larger number of samples on the boundaries of detection,

low and high, and still kind of the standard controls that you would want.

DR. SANDBERG: I am Sonja Sandberg and I support the change from Class III to II. We have been talking about benefits and risks, and as I was thinking about this the first thing was if it's working why are we going to make any change. But now that I have been hearing the discussion I can see that there are benefits. There are benefits to industry which will encourage them to perhaps come up with new products, which is then a benefit to public health.

And no one has mentioned anything about the benefit to the FDA, but certainly having to deal with less paperwork could be considered a benefit as well. On the other side of it, if it has a benefit, what would the down sides be?

But I have been convinced that the FDA has been looking carefully at what has been happening in the past, and based on that, along with some other ways to mitigate risks, that would in fact make this work. So I am in support of that.

MR. REES: I'm Robert Rees. I guess, again to save time, I agree also with the reclassification from III to II. I think, again, just addressing some of the points that have been brought up throughout the entire day -- examples

are pediatric patients -- after having that clarification of what I had read prior to the meeting and all of these proposed special controls and the details that went into it, I think that alone in the last hour allowed me to say yes, I would agree with the re-classification from a III to a II.

DR. ORTEL: Tom Ortel from Duke. I agree with the down-classification as well. Like we said earlier, there have been a lot of subpopulations, margins of the test, low positive, high positive, et cetera. All of these things need to be taken into consideration. But, recognizing the limitations of how you can do that, I still would agree with the recommendation.

DR. CALIENDO: Patricia, you are on the phone. Your thoughts?

MS. LUPOLE: I completely agree with the down-classification, and I think we are going in the right direction.

DR. LEWIS: I also support the proposed reclassification of III to II, and agree that specific controls be used to mitigate risks. In my view, I look forward to the FDA going through a deliberate process where it thinks about the likely subpopulations in which there is anticipatable heterogeneity of test performance, and urge

the agency to consider establishing either different performance boundaries for those subpopulations or clinical settings or requiring the submitting sponsor to propose boundaries for those subpopulations with the rationale for their choices.

DR. DE VAN: This is Michael DeVan. I also support the down-classification.

DR. BAKER: Judith Baker. I similarly support the down-classification with particular attention to the subpopulations we previously discussed. It seems that there has been a great deal of careful consideration throughout these deliberations today and I have full confidence that moving forward we will give due consideration to all the complexities.

DR. CALIENDO: Dr. DeMaria, are you still on the line?

DR. DE MARIA: I just want to express my appreciation to the speakers because I thought the presentations were really very clear and comprehensive and the discussion was very enlightening. I agree with Dr. Caliendo that we have had a lot of experience with the tests under consideration, and the state-of-the-art of screening diagnosis and treatment of hepatitis-C has

evolved, and I think I am very comfortable with moving from Class III to Class II.

I think of these as two different questions inherent in what has been presented. The first question is the down-classification, and that has no effect on the performance of the tests at all. The tests are still what they are, and I think that with this discussion I'm convinced that the special conditions can be put in place and would provide all the important protections that Class III now provides, and the potential benefit of having new test modalities would be advantageous. Thank you.

DR. DODD: I support the downgrading from Class III to Class II. I have two comments. One, it is just remarkable to think about having sensitivity and specificity at this high a level range. You know I work in all sorts of other areas where I would be thrilled to be talking about accuracy this high, so let's not lose that.

At the same time, in reading the special controls I might appreciate more discussion about the principles behind it rather than specific numbers, because you might be in a situation where you have a higher sensitivity and lower specificity or *vice versa* and there could be another advantage to approving it. I understand you guys know what you are doing. I get the sense that you will figure this

out, but sometimes I think it is good to have comments to help you support things.

The last thing is maybe just more of my intellectual interest. I would love to hear more about what had happened with the previous two down grades, the EBV and the CMV. I think if there were any lessons learned I didn't really hear that come forward. But maybe with moving forward with the HIV testing, if there are any lessons, I still just would love to hear more about that. Thank you.

DR. KIMBERLIN: I support, as well, downgrading form Class III to Class II. I also want to express my gratitude to the members of the committee. As the only pediatrician, there are not many national committees that I sit on where everyone else mentions the word pediatrics more than I do, so I really appreciate you thinking about the children.

DR. MILLER: I also support the downgrading of the hepatitis-C tests from Class III to Class II with special controls as outlined in the Executive Summary. The only additional comment I would like to make is just to reiterate something Dr. Caliendo said a few moments ago regarding just a caution not to make the special controls too burdensome themselves that really we lose the distinction between Class III and Class II.

DR. ADEYEMI: I support the downgrading from a Class III to Class II. A lot of the rationale and concerns have been answered. As a clinician in a high prevalence inner city population, to be able to get new innovate stuff to the market will hopefully reduce the cost and get more confirmatory testing done that can then lead to care.

So I do support it knowing that there are special controls in place, and being able to look at it in different populations.

DR. THOMAS: I am also in support of the downgrading from C to B, and I am also wanting to repeat what Melissa said in terms of when the special controls are added to make sure that they don't somehow paradoxically make it more difficult to expand testing opportunities and make these tests more effective in the United States population.

DR. WARD: I also support the downgrading. As I mentioned earlier, it's important to keep the public health issues in mind. Since I am here to give the public health perspective, we basically have an under-diagnosed, under-treated disease that's a big public health problem, and we want to spur innovation to help with two problems. These were mentioned by Saleem earlier -- affordability and access.

I think, as we look at our special controls -- to get back to what Melissa said -- we want to look at controls that facilitate the innovations to correct these issues in a way that still assures quality but then is also providing some answers to the questions around affordability and access, particularly for populations that are currently marginalized, and you have to look for outreach opportunities to make testing available. Thank you.

DR. CALIENDO: I, too, am in favor of down-classifying from III to II. I think the benefit to public health exceeds the risk.

My biggest concern coming into today was the post-marketing phase and how would we keep up with and assure that tests were high quality. It is clear that the approval process is very rigorous, but I think today's discussion has been very helpful. The FDA has given us some good information and I feel that I don't have a concern with that at all.

With that, you have a unanimous decision here to down-classify.

Agenda Item: Summary and Adjourn

DR. CALIENDO: Just to summarize some of the issues, one is pediatrics, neonates, the importance of

getting data in this patient population. I think that having special consideration on the comparator test and maybe some structure around that so that we avoid using a weaker comparator test over time and accelerating that slippery slope.

The group also talked about considering different performance characteristics for point-of-care tests that may really bring a very strong benefit that would help mitigate a little bit less of a performance.

Labeling to include limitations in populations that don’t form antibody levels at the rate of a normal host, so, immunocompromised hosts.

And then some sort of approach or process for determining the number of specimens that need to be detected in subpopulations. There seemed to be interest in having some structure put around that. But I would put the caveat that we don’t want to make special controls too burdensome because it will defeat the whole purpose of why we are here today and the whole value to public health if we don’t really move the needle in reality for the manufacturers.

Uwe, I think you are left with time for a comment.

DR. SCHERF: I have to say I am happy that we were able to get together today. I think it was an excellent discussion, and I think it's interesting to see that when we try to describe some of our approaches for how to address with these special controls that are normally not in your environment, that there are really opportunities to share and exchange our knowledge and our thoughts and move certain aspects forward.

I don't want to re-summarize what you just did. You actually hit all the important points, but I might like to add that it is also interesting from some of the discussion and the presentations that we actually have a new wave of infection, so, clearly, supporting additional easily accessible devices will really help.

I need to emphasize that we want to avoid the slippery slope. That is something we cannot accept, and I think there are opportunities to address this. And again, the spectrum bias that was mentioned today many times is something that also needs to be addressed, but it looks like there seem to be opportunities to do that.

I would like to just thank everybody here, the speakers as well as the panel members, for this clear message to us. This is very helpful for us, and we will be able to move things forward and would like to thank you for

all your participation and your public health service during this panel meeting.

DR. CALIENDO: I too would like to thank everyone. I know this has been a fatiguing couple of days for people and I just appreciate everybody being here today and being on their A game and being very engaged.

Our role is to help the FDA, and I appreciate that you reach out and ask for us to meet like this because I think it is extremely helpful. So, thanks to the FDA, and thanks to the entire panel. Everybody have safe travels home. I hope you don’t spend more time in this lovely city than you had hoped.

The meeting is adjourned.

(Whereupon, the meeting was adjourned at 3:55 p.m.)