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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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MICROBIOLOGY DEVICES PANEL OF THE MEDICAL DEVICES ADVISORY

COMMITTEE (MDAC)

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Consumer Representative	Roblena E. Walker, Ph.D.	Chief Executive Officer, EMAGAHA, INC.
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Open Public Hearing Speakers	Dr. Yasmin Ibrahim	Hepatitis B Foundation
	Dr. Sue Wong	Center for Asian Health, Cooperman Barnabas Medical Center
	Dr. Diana Zuckerman	President, National Center for Health Research
	Dr. Robert Gish	Medical Director, Hepatitis B Foundation

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Call to Order and Panel Introductions

Dr. Van Der Pol: I would like to call this meeting of the Microbiology Devices panel to order. I'm Dr. Barbara Van Der Pol, the Chairperson of this panel. I'm a Professor of Medicine and Public Health at the University of Alabama at Birmingham, and I have a focus on development and evaluation of diagnostic products that detect infectious diseases. I note for the record that the members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the panel will provide preliminary input on the potential future reclassification of nucleic acid and serology based in vitro diagnostic devices indicated for use to aid in the diagnosis of hepatitis B virus, HBV, infection and/or for the use to aid in the management of HBV infected patients; serology based in vitro diagnostic devices indicated for use to aid in the detection of past, recent, or current infection with human parvovirus B19; and cell mediated immune reactivity in vitro diagnostic devices indicated for use to aid in identification of in vitro responses to peptide antigens that are associated with mycobacterium tuberculosis infection and/or for the use as detection of effector T-cells that respond to stimulation by *M. tuberculosis* agents from Class III to Class II.

Before we begin, I would like to remind the public and panelists that this is a non-voting meeting and ask our distinguished committee members and the FDA attending virtually to introduce themselves. Committee members, please turn on your video monitors, if you have not already done so, and unmute before you speak. I will call your name. Please state your area of expertise, your position, and your affiliation. I'd like to start with Dr Kathleen Beavis.

Dr. Beavis: Good morning. Thank you, Dr. Van Der Pol. I'm Kathleen Beavis. I'm a Professor of Pathology at the University of Chicago, and my main foci are tuberculosis and HIV. Thank you.

Dr. Van Der Pol: Thank you. I'd like to call on Dr. Ricardo M. La Hoz.

Dr. La Hoz: Hi. I'm Ricardo La Hoz. I'm the Director of Solid Transplant Infectious Diseases at the University of Texas Southwestern Medical Center in Dallas. I'm also an Associate Professor of Medicine, and I am a Transplant Infectious Disease Specialist.

Dr. Van Der Pol: And Dr. Thomas Moore.

Dr. Moore: Morning, everybody. I'm Dr. Tom Moore. I'm an Infectious Disease Physician in Wichita, Kansas. My area of expertise is just general infections.

Dr. Van Der Pol: Dr. Gary Procop.

Dr. Procop: Gary Procop, CEO of American Board of Pathology and Professor of Pathology at Cleveland Clinic Lerner College of Medicine, specialty in microbiology and infectious disease pathology.

Dr. Van Der Pol: Dr. Cathy Petti.

Dr. Petti: Good morning. CEO of Health Spring Global. I'm an expert in infectious diseases and clinical microbiologist.

Dr. Van Der Pol: Dr. Emily Blumberg.

Dr. Blumberg: Good morning. I'm Emily Blumberg, a Professor of Medicine at the University of Pennsylvania where I'm the Director of Transplant Infectious Diseases and of the Infectious Disease Fellowship Program, and my specialty is transplant ID.

Dr. Van Der Pol: Dr. Camille Kotton.

Dr. Kotton: Good morning. I am the Clinical Director of Transplants and Immunocompromised Host Infectious Diseases at Massachusetts General Hospital and Associate Professor at Harvard Medical School. My area of expertise is within transplants and infectious disease. Thank you.

Dr. Van Der Pol: Dr. Angie Caliendo.

Dr. Caliendo: Good morning. I'm Angie Caliendo. I'm a Professor at Brown. My expertise is in adult infectious diseases and molecular diagnostics for infectious disease.

Dr. Van Der Pol: Dr. Marcus Pereira. Did I say that right?

Dr. Pereira: Good morning. Yes. Marcus Pereira. I'm an Associate Professor of Medicine at Columbia University Medical Center and Medical Director of the Transplant Infectious Disease Program, and my area of expertise is also transplant infectious diseases.

Dr. Van Der Pol: Dr. Valerie Ng.

Dr. Ng: Good morning. I'm Valerie Ng. I'm a Professor Emeritus of the Department of Laboratory Medicine at the University of California, San Francisco. I'm currently the Lab Director and the Chair of the Department of Alameda Health System. I direct the clinical laboratories within this public health safety net organization. Thank you. I'm sorry. I'm a lab generalist.

Dr. Van Der Pol: And Dr. Charles Chiu.

Dr. Chiu: Good morning. I'm Dr. Charles Chiu. I'm a Professor in Laboratory Medicine and Infectious Diseases at University of California, San Francisco. And my area of expertise is virology and molecular diagnostics.

Van Der Pol: Dr. Nicholas Wentzensen.

Dr. Wentzensen: Good morning. I am a Senior Investigator and Deputy Director of the Clinical Genetics branch at the National Cancer Institute. My area of research is on gynecologic cancers with a strong focus on infectious disease causes of cancer, particularly HPV and other STDs where we are doing a lot of work on guidelines and a lot of assay development and validation.

Dr. Van Der Pol: Mr. Brad Spring.

Mr. Spring: Yes. Good morning. My name is Brad Spring, and I am the Head of Global Regulatory Policy and Intelligence at Roche Diagnostics, and I am the industry rep on the panel.

Dr. Van Der Pol: Dr. Roblena Walker.

Dr. Walker: Good morning. I'm Dr. Roblena Walker, CEO of Omega Hot Ink, research scientist as well. Area specialty is microbiology and infectious diseases.

Dr. Van Der Pol: Ms. Jennifer Schwartzott.

Ms. Schwartzott: Hi. I'm Jennifer Schwartzott, and I am your patient representative.

Dr. Van Der Pol: Dr. Timothy Stenzel.

Dr. Stenzel: Good morning and welcome. I'm Tim Stenzel. I direct the Office of In Vitro Diagnostics at the FDA. I am a board-certified molecular pathologist, and I have experience in infectious disease, cancer, and genetics. Thanks.

Dr. Van Der Pol: Dr. Uwe Scherf.

Dr. Scherf: Yeah. Good morning. I'm Uwe Scherf. I'm the Director of the Division of Microbiology Devices here at FDA. I've been in this position almost 10 years, and I've worked on all of the products we are discussing here today. Thanks.

Dr. Van Der Pol: And Dr. Kristian Roth.

Dr. Roth: Hello. Good morning. My name is Kris Roth. I'm the Deputy Director of the Division of Microbiology.

Dr. Van Der Pol: Thank you everybody, and now I'm going to turn this over to Candace Nalls, the Designated Federal Officer for today's Microbiology Devices Panel, and she'll make some introductory remarks.

Conflict of Interest Statement and Appointment of Non-Voting Members

Ms. Nalls: Good morning. I will now read the conflict-of-interest statement. The Food and Drug Administration, FDA, is convening today's meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee

Act, FACA, of 1972. With the exception of the industry representative, all members and consultants of the panel 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 panel's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public. FDA has determined that members and consultants of this panel are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 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 a 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 panel 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 U.S.C. section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts/grants/CRADAs, teaching/speaking/writing, patents and royalties, and primary employment.

For today's agenda, during session one, the panel will discuss and make recommendations regarding a potential future reclassification from Class III to Class II with special controls of nucleic acid and serology based in vitro diagnostic devices indicated for use to aid in diagnosis of hepatitis B virus, HBV infection, and/or for use to aid in the management of HBV infected patients. The panel, during session two, will discuss and make recommendations regarding a potential future reclassification from Class III to Class II with special controls of serology based in vitro diagnostic

devices indicated for use to aid in the detection of past, recent, or current infection with human parvovirus B19. The panel, during session three, will discuss and make recommendations regarding a potential future reclassification from Class III to Class II with special controls of cell-mediated immune reactivity in vitro diagnostic devices indicated for use to aid in identification of in vitro responses to peptide antigens that are associated with mycobacterium tuberculosis infection, and/or for use as detection of effector T-cells that respond to stimulation by *M. tuberculosis* agents.

Based on the agenda for today's meeting and all financial interests reported by the panel members and consultants, no conflict-of-interest waivers have been issued in accordance with 18 U.S.C. section 208. Mr. Bradford Spring is serving as the industry representative acting on behalf of all related industry. Mr. Spring is employed by Roche Diagnostics Corporation. We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has 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 panel of any financial relationships they may have with any firms at issue. A copy of this statement will be available for review and will be included as part of the official transcript. Thank you.

For the duration of the Microbiology Devices Panel meeting on September 7th, 2023, Dr. Roblena Walker and Ms. Jennifer Schwartzott have been appointed to serve as temporary non-voting members. For the record, Dr. Walker serves as consumer representative to the Antimicrobial Drugs Advisory Committee at the Center for Drug Evaluation and Research, CDER. Ms. Schwartzott serves as patient representative consultant to the Cellular Tissue and Gene Therapies Advisory Committee at the Center for Biologics Evaluation and Research, CBER. These individuals are special government employees who have undergone the customary conflict of

interest review and have reviewed the materials to be considered at this meeting. The appointments were authorized by Russell Fortney, Director for the Advisory Committee, Oversight, and Management Staff on 7/25/2023.

Before I turn the meeting back over to Dr. Van Der Pol, I'd like to make a few general announcements. In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak. The press contact for today's meeting is James McKinney. Thank you very much. Dr. Van Der Pol.

Dr. Van Der Pol: Thank you, Ms. Nalls. At this time, I'd like to invite Dr. Timothy Stenzel to give some opening remarks. Dr. Stenzel.

Opening Remarks — Dr. Timothy Stenzel

Dr. Stenzel: Thank you, Dr. Van Der Pol. Welcome to all who are joining us today. Your participation and/or your attention to these important topics today and tomorrow are much appreciated. I want to especially thank our panel chair, Dr. Van Der Pol, and all of the distinguished panel members and all of the FDA staff who have worked so hard to make today and tomorrow possible. Today we examine whether the FDA can safely down classify the Class III tests for hepatitis B, parvovirus, and tuberculosis. Thank you in advance for the panel's input, as well as the input we receive from the public. It is the reason for this meeting, and we look forward to hearing from you. Tomorrow we'll focus on pandemic preparedness, also a very important topic. And, again, thanks to all, and I am looking forward to two great days of panel deliberations. Thank you.

Dr. Van Der Pol: Thank you, Dr. Stenzel. At this time, I'd like to invite the FDA to start their first presentation. I'd like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel chair. FDA, you may now begin your presentation.

FDA Presentation: Overview of Device Regulation — Scott McFarland

Mr. McFarland: Hello. My name is Scott McFarland, and I'm a Regulatory Counsel within CDRH's Office of Product Evaluation and Quality. Today I will be providing a high-level overview of the medical device classification process, which forms the basis for our discussion today. The purpose of this panel meeting will be to seek recommendations from the panel members regarding the reclassification of three in vitro diagnostic IVD devices that are currently Class III, specifically whether sufficient information exists such that the development of special controls, which along with general controls, can mitigate the risk from these devices such that the devices would provide a reasonable assurance of safety and effectiveness, and, therefore, can be eligible for a Class II designation.

We begin by explaining the different classes of medical devices. Devices are classified based on the controls necessary to mitigate the risks associated with the device type. Class I devices are only subject to general controls. Class II devices are subject to both general and special controls. And Class III devices are subject to general controls and pre-market approval. These regulatory controls will be discussed in greater detail on the following slides. Importantly, a device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness.

Now, let's go into more detail about each of the classes. As mentioned previously, Class I devices are those devices for which general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. Most Class I devices do not require FDA pre-market review prior to being marketed. Slide includes a few examples of Class I devices. These include elastic bandages, handheld manual cervical instruments, and different culture mediums. There's also an alternative pathway to determine that a device is Class I. Class I devices could also be devices that cannot be classified into Class III because they're not life sustaining, life supporting,

or of substantial importance in preventing impairment of human health, and they do not present a potential unreasonable risk of illness or injury. And these devices cannot be classified into Class II because insufficient information exists to establish special controls to provide reasonable assurance, safety, and effectiveness.

As previously mentioned, general controls are basic requirements to apply to all medical devices and are outlined in the Federal Food, Drug, and Cosmetic Act. Some examples include ensuring the devices are not misbranded or adulterated, following good manufacturing practices, meeting establishment, registration, and device listing requirements, and adhering to reporting and record keeping requirements. Class II devices are those devices which cannot be classified into Class I because general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls provide such assurance.

Typically Class I devices require a pre-market notification, generally referred to as a 510(k) submission, prior to being marketed in the US. Examples of Class II devices include intravascular administration sets, for example, syringes, nucleic acid based IVDs, the detection of mycobacterium tuberculosis complex, and endoscopes. There are many types of special controls, and some examples include analytical and clinical testing, sterilization validation, and device specific labeling requirements. These special controls, in combination with the general controls previously described, provide reasonable assurance of safety and effectiveness for Class II devices. Companies must include information within their 510(k) submissions demonstrating how the special controls for the specific device type are met.

Class III devices are those which cannot be classified into Class II because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and the devices are life

sustaining or life supporting or are of substantial importance in preventing impairment of human health or present a potential unreasonable risk of illness or injury. Class III devices typically require premarket approval through a premarket approval application, PMA, prior to being marketed. Examples of Class III devices include breast implants and IVDs for the detection and differentiation of human papillomaviruses.

Here is a flowchart that walks the general decision-making process for each of the classes that was just discussed. We start with determining whether general controls are sufficient to provide reasonable assurance of safety and effectiveness. If so, the device can be appropriately regulated in Class I. If not, we ask whether there is sufficient information that allows us to be able to develop special controls that, in combination with the general controls, provide reasonable assurance of safety and effectiveness. If so, the device can be appropriately regulated in Class II. If not, then it would be Class 3 if the device is life supporting or life sustaining r if it is of substantial importance in preventing impairment of human health or if it presents a potential unreasonable risk of illness or injury. If the device is not life supporting or life sustaining or of substantial importance in preventing impairment of human health and does not present a potential unreasonable risk of illness or injury, then we end up back at a Class I designation.

What we asked in the panel today is to provide input and recommendations as to whether, one, hepatitis B virus antigen antibody and molecular assays, two, parvovirus antibody assays and, three, mycobacterium tuberculosis interferon gamma release assays should be reclassified from Class III into Class II. The input should include an identification of the risk to health presented by each device type and a discussion of whether each device is life supporting, life sustaining, of substantial importance of preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury. The panel will also be asked to discuss whether sufficient information exists to develop special controls, and what those special controls should

be, that, in combination with the general controls, would provide reasonable assurance of safety and effectiveness for each device type.

Following this panel meeting, the FDA will consider the available evidence, which includes the input received from this panel and the public and consider potential future reclassification of the device types discussed today. I hope this has provided you with sufficient background to set the stage for the forthcoming discussion. Thank you for your time and attention.

Hepatitis B Virus Assays — Dr. Maria Ines Garcia

Dr. Garcia: Hello. Today I will present on the potential hepatitis B virus, HBV, device reclassification. HBV represents a substantial public health burden. CDC estimates that chronic HBV infection in the US affects between 580,000 to 1.17 million people. Because HBV infection can be asymptomatic, many individuals are unaware of their HBV infectious status. Approximately 95 percent of adults with acute HBV infection recover completely, whereas five percent of adults develop chronic HBV. Infants born to women who are hepatitis B surface antigen positive are at high risk of HBV infection. In the absence of treatment, infants infected with HBV have a 90 percent risk of progression to chronic HBV, and up to 25 percent of infants who acquire chronic HBV infection will die prematurely.

Chronic HBV infection increases the risk of developing liver damage, liver cancer, and liver failure. In addition, HBV can be reactivated in patients receiving immunosuppressive therapies, resulting in serious risk of liver failure or liver associated death. For these reasons, diagnosis of HBV infection with HBV antibody and antigen tests is essential to ensure that patients are linked to appropriate care. Current CDC guidelines recommend screening for all adults aged 18 years and older for HBV infection at least once during their lifetime. This includes testing for

surface antigen, surface antigen antibodies, and core antigen antibodies. Pregnant people should also be screened with a surface antigen test during each pregnancy.

The table shows the different interpretations, acute infection, chronic infection, resolved infection, immune due to vaccination, and others, and the follow up actions to take based on the results of HBV antigen and antibody tests. HBV antigen assays have the following intended use where the assay may be used to screen for hepatitis B infection in pregnant women to identify neonates who are at risk for acquiring hepatitis B during the perinatal period. Assay results, in conjunction with other laboratory results and clinical information, may be used to provide presumptive evidence of infection with HBV, the state of infection or associated disease not determined in persons with signs and symptoms of hepatitis, and in persons at risk for hepatitis B infection.

Qualitative antibody assays have the following intended use where the assay may be used as an aid in the diagnosis of adults with acute or chronic hepatitis B infection and in the determination of the clinical status of HBV infected individuals in conjunction with other HBV serological markers for the laboratory diagnosis of HBV Disease associated with HBV infection. This assay can also be used as an aid in the differential diagnosis in individuals displaying signs and symptoms of hepatitis. Quantitative surface antigen antibody assays have the following intended use where the assay may be used as an aid in the determination of susceptibility to HBV infection for individuals prior to or following HBV vaccination or where vaccination status is unknown. Assay results may be used with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection. A reactive assay result will allow a differential diagnosis in individuals displaying signs and symptoms of hepatitis, in whom etiology is unknown. The detection of anti-HBS is indicative of laboratory diagnosis of seroconversion from HBV infection or from vaccination.

The risk to health for HBV antibody and antigen tests includes false negative results. These may result in misdiagnosis of infected patient, incorrect HBV infected status determination, including delay, failure to perform additional diagnostic procedures, and linkage to appropriate care, unnecessary testing in pursuit of another potential cause of hepatitis, and potential transmission of HBV to others. A way to minimize potential sources of false negatives is for the assay to have optimal sensitivity. The risk to health for HBV antibody and antigen tests also includes false positive results. These may result in misdiagnosis of infected patient, incorrect HBV infected status determination, including unnecessary diagnostic procedures, missed opportunity for vaccination, and psychological stress to the patient. A way to minimize potential sources of false positives is for the assay to have optimal specificity.

When the patient is diagnosed as HBV infected with the antibody and antigen assays, they are then tested with HBV DNA to guide treatment decisions. Because current HBV treatments are lifelong, patients receive regular HBV DNA testing. The goal of HBV treatment is sustained suppression of HBV replication, also known as undetectable HBV DNA. This leads to improved liver enzymes, loss of HBeAg, with or without detection of HBeAG antibodies, and improvement in liver histology. HBV molecular assays have the following intended use, where the assay may be used as an aid in the management of patients with chronic HBV infection undergoing antiviral therapy. The assay can be used to measure HBV DNA levels at baseline and during treatment to aid in assessing response to treatment. The results from the assay must be interpreted within the context of all relevant clinical and laboratory findings.

The risk to health for HBV molecular tests includes false negative, falsely decreased results, incorrect interpretation of test results, failing to correctly operate the test. These may result in withholding or premature discontinuation of HBV antivirals, potential transmission of HBV to others, potential for other unassisted necessary medical procedures to investigate other causes of

liver disease. A way to minimize potential sources of false negatives is for the assay to have optimal sensitivity. The risk to health for HBV molecular tests also includes false positive, falsely elevated results, incorrect interpretation of test results, failing to correctly operate the test. And these may result in administration or continuation of unnecessary antiviral treatment, psychological stress to the patient. A way to minimize potential sources of false negatives is for the assay to have optimal specificity. Special controls could potentially be developed to mitigate the risks of false positive, false negative, incorrect results interpretation, and failure to correctly operate the device. The goal is to maintain consistently high performance across devices with similar intended uses and for individual devices of the total product lifecycle.

The following slide shows the questions for the panel to discuss. I will read each one. One, please comment on whether you believe FDA has identified a complete and accurate list of risks to health presented by the following devices: Qualitative HBV antigen tests, qualitative HBV antibody tests, quantitative anti-HBS tests, and/or quantitative HBV molecular tests. Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risks should be included in the overall risk assessment of the devices listed above. Two, please discuss potential mitigation measures/controls that FDA should consider that could mitigate each of the identified risks. Three, based upon the information presented and future discussion at this panel meeting, please discuss whether, based on the available information, the panel believes FDA should initiate the reclassification process for these devices from Class III to Class II, subject to special controls. Four, currently there are no FDA authorized tests for the detection and quantitation of hepatitis B surface antigen. Please discuss appropriate intended use for such a device, potential risks associated with that intended use, and whether mitigation measures/special controls could be developed that, in addition to general controls, mitigate risks to health. Thank you.

Open Public Hearing

Dr. Van Der Pol: We will now proceed to the open public hearing portion of this meeting. Public attendees are given an opportunity to address the panel to present data, information, or views relevant to the meeting agenda. Ms. Nalls will read the open public hearing disclosure process statement.

Ms. Nalls: Both the Food and Drug Administration, FDA, 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 meeting, 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, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Dr. Van Der Pol: Thank you, Ms. Nalls. FDA has received four requests for the open public hearing portion. Each speaker will be given five minutes to speak, and we will begin with Dr. Yasmin Ibrahim.

Dr. Ibrahim: Hello. This is Yasmin Ibrahim, a Public Health Program Director at the Hepatitis B Foundation located in Doylestown, Pennsylvania. Dear committee members, currently only laboratory-based hepatitis B diagnostics are approved, meaning a blood draw must be taken and analyzed in a lab. This means multiple visits are needed to diagnose hepatitis B, which is a

significant barrier for those groups that are most impacted by hepatitis B, like communities of color, foreign born communities, the LGBTQ community, and people who use drugs. Blood draws are associated with increased costs, can be logistically difficult to perform, and low-threshold care settings, such as syringe services, programs of community-based care, and impacted communities, are often hesitant to draw blood. Additionally, there is lag time, which increases loss to follow up while waiting for days for test results, particularly in community screening settings where a large percentage of screening of high-risk people takes place.

In 2023, the Centers for Disease Control and Prevention recommended that all adults aged 18 years and older should be screened at least once in their lifetime using a triple panel test. This recommendation aligns with the US Department of Health and Human Services plan to eliminate hepatitis B in the United States. This new recommendation provides an ideal opportunity to improve hepatitis B diagnosis rates in the United States. And we strongly believe that hepatitis B point of care rapid diagnostic tests are necessary to implement these recommendations and could be a catalyst to scaling up hepatitis B screening. Point of care rapid diagnostic tests will allow us to address current challenges and improve hepatitis B diagnosis across the United States to move infected people into life-saving care and treatment and play a critical role in reaching the goals of viral hepatitis elimination in the United States.

Here are a few highlights about the burden of chronic hepatitis B in the United States. Up to 2. 4 million people in the United States are chronically infected with hepatitis B; and without timely diagnosis and treatment, 25 percent will die prematurely from liver cancer. Currently up to 70 percent of people with chronic hepatitis B infection in the United States remain non-diagnosed. At the same time, we are seeing a troubling increase in new acute hepatitis B cases in many states largely associated with the opioid crises among people who use drugs, which is another population that has limited health care access. Hepatitis B disproportionately impacts Asian Americans,

Pacific Islanders, Native Hawaiians, and people of African origin. These primarily immigrant and refugee communities face unique barriers to prevention and care and hold their own unique set of social determinants that lead to reduced access to healthcare, stigma and discrimination, and serve as barriers to diagnosis. Access to rapid diagnostic tests for hepatitis B would reduce delays and complexity due to phlebotomy and laboratory testing.

Additionally, there are benefits to early diagnosis of chronic hepatitis B. Hepatitis B damages the liver over time. Even without alarming symptoms, hepatitis B can lead to cirrhosis and liver cancer. Additionally, recent research indicates that hepatitis B viral DNA integrates into the host genome early and consistently throughout the infection. Access to timely diagnosis is an essential step in managing hepatitis B and improving health outcomes of those impacted by the disease. Upon diagnosis, individuals with chronic hepatitis B must be evaluated and advised on a proper management plan. Antiviral therapy controls viral replication to help prevent hepatitis B related liver disease like cirrhosis, liver cancer, and premature death. Similar to people living with HIV/AIDS, people living with chronic hepatitis B are expected to live long, healthy lives if they gain access to timely care. To this end, we respectfully request that the Food and Drug Administration consider the reclassification of hepatitis B testing from the current Class III to Class II. Thank you.

Dr. Van Der Pol: Thank you. We'll now hear from Dr. Sue Wong. Dr. Wong, go ahead.

Dr. Wong: Great. Thank you. Let me just get my slide. Sorry. Of course, I can't find it now. That's fine. I'll go ahead. Dear committee members, thank you so much for having me. My conflict of interest includes a Gilead grant that funds my institution for our research project that I have. I'm a practicing internist, and I'm Director for the Viral Hepatitis Programs and the Center for Asian Health at the Cooperman Barnabas Medical Center in New Jersey. I'm also living with hepatitis B, and I'm former president of the World Hepatitis Alliance, which is an NGO dedicated to harnessing

the power of people living with viral hepatitis to achieve its elimination. I also serve as Senior Advisor of Global Health to the Hepatitis B Foundation.

In 2016, WHO set forth the goal of eliminating hepatitis B as a public health problem by 2030. This is an achievable milestone because we have tools to eliminate hepatitis B. We have ways of testing people, we have effective vaccines, and we have treatments to suppress the virus to prevent end stage liver disease, liver cancer, and prevent transmission. And Hepatitis B elimination would be a very impactful achievement. Globally, hepatitis B is the most common chronic bloodborne infection. There are 350 million people in the world living with hepatitis B. That's seven times more than those living with hep C and almost 10 times more than people with HIV. Yet only 10 percent of these 350 million have been diagnosed. The vast majority of people largely unaware of having this infection.

The need to scale up testing is one of our largest gaps to achieving elimination. Without being diagnosed, people living with hep B cannot get care or treatment to reduce the risk of liver cancer or the risk of transmission. In the US up to 2. 2 million people are living with hep B, and about two thirds of them remain undiagnosed. More than 50 percent of people living with hep B in the US are Asian American Pacific Islanders, and 12 percent are African in origin. It is well documented that many of these communities face significant barriers to accessing health care in our country. Down classifying hepatitis B assays would be instrumental to increasing access to testing, and it would be an enabler for the US to achieve our goals set forth in the HHS Viral Hepatitis National Strategic plan. It would allow for more manufacturers to seek approval for tests, and it would expand our testing options, which is much needed.

Point of care, rapid diagnostic tests for hepatitis B surface antigen have existed for years and are approved for use in other countries. At least two that exist are already on the WHO pre-qualified list, and others also have high sensitivity and high specificity. These tests are used around

the world and have increased the reach of testing efforts. Many cost as little as a dollar a test and do not require phlebotomist or expensive lab equipment. Yet none of these are FDA approved, and thus not available in the US. There are numerous publications that show the effectiveness of point of care tests and also their use in various settings. Point of care tests allow for health care in low barrier settings such as community clinics, health fairs, and other community-based settings. These are especially important in populations that face significant hurdles to accessing medical services, maybe due to geography, lack of insurance, lack of transportation, child care, or work that doesn't allow them to leave during office hours or limited English proficiency.

Rapid diagnostic testing also importantly allows for testing and diagnosis to occur at the same time. Patients know the results of the test shortly after being tested. There is no prolonged anxiety from waiting, and they do not have to arrange the logistics of getting the result, which could be another appointment, they have to take time away from work, a phone call that they miss, or a letter that they may not be able to understand. This is critical for patient-centered care. Once people know that they have hep B, they can begin taking care of themselves. They can educate themselves. They can make an appointment for hepatitis B care, get additional testing to see if they need treatment, which will include the hep B DNA test and other liver studies, and they can begin protecting their liver. They can limit alcohol use and herbal medications. And they can begin discussing with their loved ones, including family members and sexual partners. One of the many struggles currently with testing is reaching people to notify them of their test results, and point of care tests would really help with the loss of follow up.

Additional HBV assays, and maybe we could change the terminology to tests, as was done for hep C, include qualitative and quantitative hep B antibody tests and quantitative hep B molecular tests. Down-classifying these as well will help with identifying whether people are immune to hepatitis B. And if they're not immune, they should be vaccinated following the recent

CDC updated recommendations for universal vaccination. Down-classifying the hep B DNA tests will be helpful, as this is necessary for evaluating the need for antiviral treatment. We also anticipate that there will be point of care and hep B DNA tests developed in the near future.

Dr. Van Der Pol: Dr. Wong, you're at time.

Dr. Wong: Okay. I just have one sentence. FDA has down-regulated hep C and HIV tests to Class II, and we believe that the safety and effectiveness criteria that allow for these also apply to hepatitis B tests. In conclusion, many of us in the hep B provider, patient, and affected communities have been long awaiting this down-classification of hep B tests. We believe this will play a critical role in expanding hep B testing and close the gaps in hep B diagnosis and care so that we can make hep B elimination a reality. Thanks.

Dr. Van Der Pol: Thank you. And now we'll hear from Dr. Diana Zuckerman.

Dr. Zuckerman: Thank you so much. Can you hear me?

Dr. Van Der Pol: Yep.

Dr. Zuckerman: Great. I'm Dr. Diana Zuckerman. I'm President of the National Center for Health Research. Our non-profit health think tank, public health think tank, was founded in 1999, and we focus on the safety and effectiveness of medical products. We do not accept funding from companies that make the products that we evaluate, so I have no conflicts of interest. My expertise is in epidemiology and public health, and I previously was a researcher at Harvard and Yale and a Congressional Investigator in the US House of Representatives and the Senate, where I evaluated the impact of FDA policies. I've published numerous articles regarding the impact of FDA policies, and I'm a founding board member of the Alliance for a Stronger FDA, which is a coalition of industry and non-profit organizations that work together to ensure sufficient resources for FDA to support its very important work.

So I want to start by thanking all of you for your important work today. And I'm going to speak briefly this morning about your goals of the meeting today. As you know, these assays have been designated as high-risk Class III devices that patients depend on for accuracy, sensitivity, and specificity. And you've heard about that this morning. I've conducted numerous studies on device recalls and have found that Class III devices are much less likely to be recalled than Class II devices because the standards for getting them on the market is much lower for Class II. The FDA does not refer to Class II devices as approved. They are referred to as cleared for market, and there's a good reason for that distinction. And that's what concerns me today.

I am not an expert on the assays being discussed today, but I have spoken with experts from medical schools and the NIH and learned that these assays already exist, as you've heard already. And so what's the need for changing the category to Class II? Lowering the standards in an effort to get them to market more quickly without the data needed to know how accurate they are is potentially very harmful to patients, either because of false positives or false negatives, resulting in inappropriate treatment. And you've heard from everyone about how important that treatment is. So, in conclusion, these assays are very important, and they're going to have an enormous impact on treatment decisions for patients. And although special controls can help improve accuracy, they aren't the same thing as the standards for a Class III device. And for that reason, I respectfully suggest that you think very carefully about whether lowering the classification is really in the best interest of patients. Thank you very much for the opportunity to speak today.

Dr. Van Der Pol: Thank you. And, finally, we'll hear from Dr. Robert Gish.

Dr. Gish: Good morning. Is audio and video okay?

Dr. Van Der Pol: Yep. You're good.

Dr. Gish: Thank you so much for having me here. I really want to thank the committee for having this open comment session. I am Robert Gish. I'm a hepatologist. I'm based in San Diego.

I'm the Medical Director of the Hepatitis B Foundation. I'm also the Medical Director of a local organization called the Asian Pacific Health Foundation. My disclosures are consultancies for Gilead and a number of other hepatitis B companies in the therapeutic space. I'm very committed to hepatitis B cure and also work in the diagnostic space.

I want to give just a little bit of history to this down-classification. I was honored to be invited and visit the FDA over a decade ago with Dr. Robert Perillo and Dr. Tim Block, asking about the steps for down-classification. We invited two diagnostic companies to be at that meeting, and one declined to come to the meeting within 24-hour notice and the other came. But after that meeting, we didn't hear from them again because they were looking at and discussing the barriers of entry of a Class III designation for hepatitis B testing. I think this is a very important issue about getting diagnostic companies into this space. I want to give another personal perspective, and that is I've worked on hepatitis B elimination in over 70 countries worldwide. In the last six months, I've been in many countries in Southeast Asia. And two weeks ago, I spent a week in China working on and surveying what would be the impact of a rapid test in the community.

One of the things that's very important in the hepatitis B world is the issue of stigma and discrimination. You've heard from Dr. Ibrahim and Dr. Wong all the important issues that I think are key to this down-classification. But part of the reason there's not broad-based recommendations about testing is the issue of stigma and discrimination. And I believe the down-classification and bringing rapid tests and point of care tests available to patients and individuals in private settings will be very important. The next step beyond that of testing in a setting where you have a medical provider is at home testing, and at home testing can be definitely catalyzed by having a rapid test available. We have apps. We have artificial intelligence. We have many other techniques now to help interpret these tests. So, individuals can test themselves and make steps individually, not necessarily having their hepatitis B tests in a public setting.

We believe that stigma and discrimination are also reasons to lead to hepatitis B cure and global elimination. Yes, hepatitis B cure will help decrease liver cancer, cirrhosis, transplant, and deaths. We want our patients, our individuals in the public setting, to be able to work in a number of different occupations. We want people to have normal lives and relationships and down-classification is important. In San Diego, we do screening in a number of immigrant communities; and having to do a finger stick for hepatitis C and then a blood draw for hepatitis B and then trying to find the patients one to two weeks later to communicate the results, interpret the results, and bring those results to a linkage to care is a multi-step process and leads to a significant dropout of patients being linked to care. We really want this down-classification to impact our patients and our providers in the US, including the pharmacists, who I think will be a key part of rapid test distribution, education, and interpretation, but also this affects the world. In each country where I've met with regulatory and commercial providers, they always ask the question is your test FDA cleared or will your test be FDA cleared in the near future? What is the path forward? If we had that green light from the FDA, clearance would affect not just our patients and providers in the US but affect individuals globally.

I want to thank you for having me here today and allowing me to put this professional and personal note on top of what Dr. Ibrahim and Dr. Wong provided. I think these are very important issues for the down-classification. Thank you so much.

Dr. Van Der Pol: Thank you. Does anyone on the panel have any questions for our open public hearing speakers? If you do, please use the raise hand function.

Dr. Van Der Pol: Okay. Let's start with Dr. Wentzensen.

Dr. Wentzensen: I actually have a question for clarification to the FDA because we've heard what I think is a little bit of a conflation between point of care testing and the device classification, and I just wanted to hear whether it is correct that these are two separate issues. I think there are

Class III devices that are point of care tests, and they're Class II devices that are not. So I just wanted to hear clarification on that.

Dr. Stanzel: Yes. Tim Stanzel. I'm happy to clarify. Yes. There's nothing that prevents a Class III device from becoming a point of care or even an over-the-counter test. In fact, the over-the-counter HIV test is a Class III test. So I did hear that potential confusion here, and I'm happy to clarify that. Thank you so much for the question.

Dr. Van Der Pol: Thank you. Dr Beavis. You're on mute. You're still muted.

Dr. Beavis: Thank you. Yeah, my question was along the same lines, and it's been answered that there's nothing that keeps a point of care from applying as a Class III. So thank you.

Dr. Van Der Pol: Any other questions?

Dr. Pereira: Yes. Marcus Pereira here. Somebody had mentioned that HIV testing is Class II, and maybe we'll be talking more about this later, but can somebody clarify sort of what parts of the HIV testing sort of menu are Class II and which ones are Class III? Thank you.

Dr. Stanzel: Yes. HIV devices are regulated by CBER. So I'm not sure if we have anybody from CBER who wants to respond to that today. If not, I can do my best attempt. So my understanding is that over-the-counter tests for HIV are still Class III. But all other tests for HIV are Class II. That is the present situation as far as I understand it. Thank you.

Dr. Van Der Pol: Any other questions? Then I now pronounce the open public hearing session to be officially closed. We will take a break at this time. We're slightly ahead of schedule. So why don't we take a 15-minute break, and that will put us back here at 10 after the hour, if you will rejoin us at that time. Thank you.

Panel Questions and Deliberation

Dr. Van Der Pol: Okay. Welcome back, everyone. It is now 10 after the hour, and I'd like to resume this panel meeting. At this time before we begin deliberations, does anyone on the panel have any clarifying questions for the FDA? Please use the raise your hand button, and I'll call on you in the order I see your hand come up.

Seeing no questions, we're going to move forward. And from here forward, we will focus our discussion on the FDA questions that were provided to us. Panel members, you have copies of these questions in your packet. We will briefly display the questions and discuss them one at a time. Please don't forget that when you are called upon, reiterate your name and your organization to make sure that the transcription can capture who's speaking. So, if you'd show the first question, please.

Question One

Dr. Van Der Pol: Okay. So the first question is to comment on whether you believe the FDA has identified a complete and accurate list of the risks to health presented by the following devices. Please comment on whether you disagree with the inclusion of any of these risks or whether you believe any additional risks should be included in the overall assessment. So with that, I'll take input from the panel. As I said, please just raise your hand. Does everyone have any thoughts about the risks as described, being concerns about false negatives and what happens in those cases, concerns about false positives?

Dr. Ng: I'm sorry, Bobby. This is Valerie Ng. I would like to add one more risk.

Dr. Van Der Pol: Go ahead, please.

Dr. Ng: And the risk is related and it's overlaid, which is testing performed as point of care.

Dr. Van Der Pol: And what do you see that risk as, aside from the performance of the actual assay?

Dr. Ng: It is sort of a common observation that test performance is not the same when testing is performed as point of care, and that relates to environmental, as well as personnel. So the engineering of these devices must be incredibly strong to mitigate those risks.

Dr. Van Der Pol: And I'm not clear, and I would love for someone from the FDA to weigh in. I know this is the panel discussion portion, but for a clarification perspective, we're not really discussing point of care tests. We're really discussing the risks of moving from Class III to Class II. And I know that, as we described already, the public speakers were focused on point of care test, but a Class III can be a point of care test. So that's not really quite to the point of our discussion. But if the FDA would like to hear more about that topic, Dr. Stenzel, maybe you can respond to that.

Dr. Stenzel: Yeah, Tim Stenzel. Yeah, so the focus for this question are the lists of risks complete and accurate? I will just say that I think the FDA welcomes the input from Dr. Ng that there could be risks based on certain technologies that need to be included. When you look to mitigate risks, as explained, that it could be point of care but also be over-the-counter relative to central lab. So I think that input is valuable. And we thank Dr. Ng.

Dr. Van Der Pol: So I see Dr. Wentzensen has his hand raised as well.

Dr. Wentzensen: Yes. Thank you. I think it would be very helpful, as you move forward with this decision process, to try to quantify these risks as much as possible and kind of maybe generate like a simple model that allows to input different assumptions, like a certain reduction in sensitivity would have the following impact on a specific indication. Some of these tests are applied widely in the population. Some in very specific settings. Some have direct consequences related to treatment. Others are to monitor an active infection. I think qualitatively that that list is good. It could be expanded, but I think the quantitative pieces of that are very important for these considerations. It reminds me of some discussions we have on HBV testing and self-sampling

where we see a small reduction in sensitivity, there's still a net benefit of expanding the reach of testing. But if that's bigger, then there is kind of equal poison, et cetera. So I think quantification of these risks to me is very important.

Dr. Van Der Pol: And using Chair's prerogative, I'll just respond to that to say that I think one of the things that's not on this list of risks is the list of benefits, and I think that that risk benefit ratio is quite an important consideration, which is partly what I think you're getting at

Dr. Wentzensen. Let me call on Ms. Schwartzott. You're next.

Ms. Schwartzott: Jennifer Schwartzott, patient representative. I wondered what the percentages of false negatives and false positives are in the Class III testings, assays, and also if anybody knows what those same percentages are in the Class II similar tests that are already on the market.

Dr. Van Der Pol: That's a great question. I'm not sure if anybody has the data.

Dr. Stenzel: Well, yeah, this is Tim Stenzel. I might call on one of my colleagues from the office to see if they can add to this. So, no test is perfect, whether it's Class III or Class II or Class I, point of care, central lab, or over-the-counter. It's all about assigning the proper risk and mitigating any risk. Those mitigations can be technical. They can be through training. They can be through labeling. So in all cases, we hope to get the best possible test performance that is possible for a given analyte. Some analytes are more difficult than others. So I don't personally have a compilation of the performance. I don't know if anybody from the Office of Major Diagnostics is comfortable enough responding specifically to this question. Ines just came on camera. But we do look at the risks versus the benefits, as has been mentioned, and we do take it into account. But as no test is perfect, we always look at mitigations.

Ines, do you have something to add?

Dr. Garcia: Sure. Yeah. To give you an idea, our current Class III products, the performance for sensitivity is about 98% and specificity is 99%. So the tests are specific and sensitive as well. So to give you an idea of the likelihood of getting a false positive or a false negative result there, we try to minimize that with these Class III devices.

Dr. Stenzel: And it looks like Uwe has come on camera. Uwe, would you like to share?

Dr. Scherf: Yeah. Uwe Scherf. Just one additional point to add to the communication. I would like to emphasize that the down-classification does not imply that we are expecting a difference in performance. So what Ines just mentioned is we have these high-performing devices that are currently brought to market via PMA, pre-market approval, but we are not expecting that a 510(k) approach would then be coming to a scenario where the performance is lowered.

Dr. Van Der Pol: Exactly right. Ms. Schwartzott, did that enter answer your questions? You're muted, but your hand is still up so I want to make sure.

Ms. Schwartzott: Yes, it does. Thank you.

Dr. Van Der Pol: All right. Dr. Pereira, and I know I keep messing your name up. I apologize.

Dr. Pereira: Oh, that's okay. Marcus Pereira here from Columbia University. So I think the main question I think that many of us have had, and I think it revolves around sort of these standards in terms of false positive and false negatives and sort of what are some of the minimum criteria for approval for test performance regarding Class III and Class II, it sounds like, I'm interpreting this, that there's no minimum standard but also no difference in expectations or requirements, at least in terms of test performance, between Class III and Class II. At least that's how I'm interpreting things. Is that correct then?

Dr. Stenzel: So, when we write the special controls for something that can be down-classified, we can put those performance expectations into those special controls. Uwe, I'm sorry. I may have interrupted you. Did you want to add anything?

Dr. Scherf: No, you have not interrupted me. Uwe Scherf again. Tim, this is exactly what I also wanted to share. The opportunities for us at FDA to capture necessary informational pieces in the special controls, and they can be related very specifically to performance. And that's something that I think normally is not known in the diagnostic community because we're not doing this every day. But we have again that tool in our hands, and we have used it several times.

Dr. Pereira: That's good.

Dr. Stenzel: I'll just clarify that for everybody who's attending today, if they don't know what special controls are, this is a document that would be generated when the down-classification process goes through in order to translate the expectations into written form for developers. The FDA then uses those special controls as a guide to determine whether a 510(k) submission is sufficient for authorization.

Dr. Van Der Pol: And I will remind the panel that question number two, because you're not seeing them all in front of you, but question two is actually going to get onto this topic exactly, which is how to mitigate those risks. So I want to stick with question one, just to make sure that I've heard everyone, and we've all had a chance to speak about, do you think this list of risks is comprehensive? Is there anything on here you think shouldn't be on here, or is there anything you want to add?

Dr. Pereira: I think it was mentioned in the summary, but I'm not sure if it was mentioned in the slides. So regarding for hepatitis B in particular and the sort of test performance, whether a false negative or false positive particular surface antibody result would lead to either unnecessary vaccination or not vaccinating someone when they would be eligible for the vaccine, I think that was mentioned, but I want to make sure that that's included.

Dr. Van Der Pol: Okay. I'll take a note of that, and I'll go next to Angie You put your hand down. Did you still have a question, or has it been answered?

Dr. Caliendo: No. I just wanted to make the point about there's no reason that the sensitivity or specificity requirements would change just because it was down-classified, and that's already been said.

Dr. Van Der Pol: Okay. Dr. Blumberg.

Dr. Blumberg: Right. Emily Blumberg, University of Pennsylvania. It seems to me, from hearing from the public comment, that the main concern from the public is access to care. And access so that leaving these as Class III, is there a greater risk that fewer people will be tested? And I'm not sure, but I think that's probably related primarily to the cost of bringing the test online. So the one thing I would add is whether leaving them as Class III will limit access to these tests.

Dr. Van Der Pol: I think I would re-emphasize what some of the panel members said is that there are many tests that are available X US that people haven't tried to get through. The PMA process, it's not just the cost, but there's a lot associated with it, including the post marketing efforts that one has to go to, to keep that approval in place. And I think that it's not just about who can afford to do what, but it's whether or not we really want to encourage more market competition by making it somewhat easier to get through the process because that helps public health overall. But the risks, I don't think, are affected by that, so sticking with that risk conversation. Dr. Moore.

Dr. Moore: Yeah. Thank you. My question, and I don't know whether this is something that could be provided here today. I know that CBER is in charge of the HIV testing, but I know some of these other discussions, same discussions, have been had with HIV testing going from level III to level II. And I wondered if there was somebody who was involved in some of those discussions who could help inform our debate today, provide some background.

Dr. Van Der Pol: Is there someone with the FDA who was involved with any of those changes in classification?

Dr. Stanzel: This is Tim Stanzel. Ines or Uwe, do you want to add anything? I would just state that we take this risk-based examination on analyte by analyte. So what was done for HIV may not be completely overlapping and appropriate necessarily for HBV. We do know that other than OTC diagnostic devices for HIV were down-classified. We know that result. But, Ines or Uwe, anything to add?

Dr. Garcia: Yes. I would echo what Tim said. We do take into consideration everything that is discussed in the panel for deciding whether the reclassification process should proceed for HBV, as well as in putting together those special controls. We also take into consideration the whole HBV environment, you know, the need for the availability of specific tests, the therapies that are available, medical practice, and we have discussions with other experts to put all of this in development.

Dr. Moore: Thank you. I know it's apples and oranges, but the thought process is similar. So thank you.

Dr. Stanzel: Yeah. I appreciate the discussion. This is Tim Stanzel. I would just add that we've already down-classified HCV, which is maybe more closely aligned with HBV than HIV.

Dr. Van Der Pol: Dr. La Hoz.

Dr. La Hoz: So if I understand correctly, we have a fair amount of information regarding the performance of hepatitis B testing currently classified as III, and the diagnostic performance being quoted, 98 sensitivity, 99 specificity. And on the other hand, we have a risk to the population, those that may have a lack of access to care, where if there were more availability for testing, they could be diagnosed promptly, engaged in care earlier, and then subsequently prevent some of the long-term complications of hepatitis B, which are liver damage, pathocellular carcinoma, and liver failure, as it's been quoted. So, I think that, to me, the risks have been outlined, and I can currently not think of an additional risk to add. And it appears that if we are going to put adequate

performance standards, we're going to have post-marketing surveillance to ensure that the IVDs continue to perform at the same standard, and it's going to increase the availability of testing. It appears that the pros of potentially downgrading will be larger than the cons.

Dr. Van Der Pol: Thank you. Dr. Caliendo.

Dr. Caliendo: Angie Caliendo, Brown. I want to go back to what Emily said, and, Barbara, I may not have understood your response. But I do think keeping it as a Class III, the risk is reducing access to care. And is that not something we would add under the risks of? I mean, I might have misunderstood when you said that really wasn't.

Dr. Van Der Pol: Well, it may be a benefit. I mean, it depends on how you look at things, right?

Dr. Caliendo: Well, we're not listing benefits.

Dr. Van Der Pol: Well, we will. Well, you're right. We're not. And, you know, my personal bias is any test not done is a test that's failed. So restricting access is a huge risk to the population as a whole.

Dr. Caliendo: Right.

Dr. Van Der Pol: So I agree with you.

Dr. Caliendo: We need to add. Yeah.

Dr. Van Der Pol: So, yeah. Okay. I'll put that in my list. The risk to public health of limited access.

Dr. Kotton: Camille Kotton, Massachusetts General Hospital. I just wanted to bring up --

Dr. Van Der Pol: Can I pause you for a second? Oh, yes. You are next. I'm sorry. I thought Dr. Bradford was next, but you are next. So sorry. Let me un-interrupt.

Dr. Kotton: I wouldn't do cuts on Zoom. Sorry. So Camille Kotton, Mass General. In general, I am in favor of downgrading, I think that there are a lot of advantages. One of the issues I wanted

to highlight that's something that I find really occasionally upsetting clinically is when we give a hepatitis B vaccine, we can actually detect vaccineemia for up to two weeks or so after they receive a vaccine. So I could envision someone for some reason getting hepatitis B vaccine, and then maybe thinking a lot about hepatitis B and getting point of care test that might suggest that they have positive hepatitis B surface antigen, which in my clinical world is always kind of a dramatic diagnosis, especially when they've been negative, negative, negative, and then all of a sudden are positive because, you know, we think that's real hepatitis B, but it turns out it's just vaccineemia. So somewhere in the package insert or elsewhere, I would want this issue to be --

Dr. Van Der Pol: Can I ask you to hold this? The next question is about mitigations, and that's exactly where this should go. So if I call on you first when we come to the next question, and let me see if, Brad, did you have anything else that you wanted to add on risks?

Mr. Spring: Yeah.

Dr. Van Der Pol: And then I will summarize risks. Because it's clear we all want to talk about mitigation.

Mr. Spring: Yeah. That's why I've been raising and lowering my hand. Brad Spring with Roche Diagnostics. A point of clarification for FDA, because I think there's a future question on here too around expanding or changing intended uses. So in light of looking at the risks associated with these tests and down-classification, is the assumption that the intended use is not changing? And I'm assuming yes, but you can answer in the affirmative or negative. But I think looking ahead, some of these tests may see a change in their intended use, and should we be considering that when we also think of down-classification and risk associated? I know you can't think of them all just because it may be somewhat infinite the possibilities, but just want to see if there's any clarification you can provide on some of the decisions we're making today based on that statement. Yeah, Tim.

Dr. Stanzel: Yeah. I'll start. Tim Stanzel. So it could be the sample types change, settings change. So that would change intended use statements. So those are potential risk mitigation opportunities for sure. And we certainly take that into account as we assess a new test. And we'd want to put as much as we can into the special controls. Ines, it looks like you've come up. You may have something additional there.

Dr. Garcia: Sure. Yeah. So our intended uses are adaptable. They're dependent a lot on medical practice or anticipated changes to medical practice. We also develop the intended use in conjunction with how the clinical study is performed. So, a big part of the intended use is its support by the clinical study. So there is flexibility there.

Mr. Spring: Yeah. Okay. No. That's good. It was just around the impact of a new intended use affecting the classification decision. And maybe this is something we can hold to the last question.

Dr. Van Der Pol: Dr. Stenzel.

Dr. Stenzel: Yeah. I just wanted to add there's some discussion about whether y'all can discuss benefits, and the FDA team would really appreciate benefit discussion in this at any point that, Dr. Van Der Pol, you deem it appropriate today, and not just for this analyte, for all the end words.

Dr. Van Der Pol: Thank you. I think that's really critical. I'm going to try and summarize so that we can go on to the mitigations, because I think that's one of the places where everybody has a lot of input that's at the tip of their tongues.

So, Dr. Stenzel, with regard to question one, I think the panel generally believes that the risks are predominantly inclusive and exhaustive. So, the two things that the panel had concerns about was that some of those risks needed to be quantified, and I'm going to paraphrase. But one of the things that I heard was that those risks may be use case dependent. And so, for example, for people who have just been vaccinated, the risk is different, obviously, and for very low prevalence populations, obviously, your positive predictive value changes. So the sensitivity and specificity

have different impacts. Even though they don't change, they have different impacts in different populations. So I think that while the risks that you've covered are comprehensive, they might need to be sort of restructured in the thinking to provide a little bit more detail for people. And then I think that, given the information that we had about the performance of current Class III tests, it sounds like those risks have been in part addressed by having really high-quality assays, and that would move us on to question two.

Question Two

Dr. Van Der Pol: So if we could put question two up on the screen just to remind everybody. This is the point at which we should discuss the mitigation measures and controls, and so mitigation measures can be describing what populations it's appropriate to use these or what clinical context it's appropriate to use these. Controls can also include setting a minimum sensitivity or minimum specificity that the assay would have to hit. So it's not related to Class III that they have to have high sensitivity specificity. Class II assays can be required to have the same performance levels. And I think that this is the point at which we should also discuss benefits, because the benefits obviously might not mitigate the risks but maybe outweigh the risk to an extent that we think that it's worth talking about those at this point.

I'd like to start with Dr. Kotton, since I interrupted her twice already.

Dr. Kotton: Thanks. So I just wanted to bring up the issue of hepatitis B surface antigen positivity within one to two weeks after receiving vaccine, which happens, I would say, in my institution happens several times a year. And if this were outside of a standard medical context, there might be concern about the diagnosis of acute hepatitis B in that it sure does seem to look like it. Although there, with this point of peer testing, there wouldn't necessarily be LFTs in clinical interpretation. So, I just wanted to highlight that this is a potential major issue that would seem like it should be covered in the package insert or other consumer-based education or other areas

that the FDA and others might think are important, but just an area where I think we should consider risk mitigation. It's beyond my area of expertise, but I don't believe that altering thresholds for positivity or things like that would really be able to handle this problem, but happy to hear what others might have to say. Thank you.

Dr. Van Der Pol: You're probably right about that, and I think that I'm going to remind the group once again that down regulating from Class III to Class II does not mean we're talking only about point of care tests. These might still be laboratory tests. And so it may be the point of care tests need even different special controls. And that's for the agency to work through their process. I think I'll go on to Dr. Procop.

Dr. Procop: Hi. Thanks so much. Gary Procop, American Board of Pathology. Just a couple of points: One was we talked earlier about it doesn't necessarily mean that the performance standard can be lowered. I think when we're entering these conversations about whether we should reclassify, it would be great to open with lower performance standards will not be accepted. You know, the performance standards will have to be as good as they were at Class III. The other point is I really did appreciate the point earlier about differences in special controls with respect to point of care testing versus laboratory testing, because we do know there are some differences in reliability, depending on who's actually doing those tests. One of the things that would be helpful, and I know this might be getting into the weeds too early, but when we consider some of these specific tests, it would be useful to know what the specific special controls might be that would ensure that quality. Just some thoughts. Thank you.

Dr. Van Der Pol: One of the special controls, I don't know if it's a special control, and I'd like the FDA's opinion. But one of the issues is obviously that it might never receive a clear waiver. So it still might require laboratory trained technologists to run the test, even if it's at the point of care.

Because remember, a point of care doesn't mean that an untrained person can necessarily run it. So, Dr. Stenzel, did you have thoughts you wanted to add about that?

Dr. Stenzel: Yeah. So we can write special controls. First of all, the presumed or the baseline classification for any new analyte that the FDA hasn't seen before is a Class III. We can, when we interact with a test developer, decide, even from the very beginning, that we have enough knowledge to write special controls to justify a de novo pathway, which will lead from the baseline state of a Class III to Class II with special controls. And when we write those special controls, whether we're in the process of down-classifying that we might do for any of the analytes today, or when we originally on the first developer interactions, we decide that it is okay to be a Class II device. We can write special controls for all different situations, whether it's central lab, point of care, and/or over-the-counter. We can write them if we feel like we can have one regulation and put it all into the special controls. We can do that if we feel like we have enough knowledge about the various risks and mitigations to justify that. And then the special controls will take that into account, whether the setting is central lab, point of care, and/or among different sample types to different clinical uses. Thank you.

Dr. Procop: Thank you.

Dr. Van Der Pol: Thank you. Dr. Beavis.

Dr. Beavis: Thank you. Kathleen Beavis from the University of Chicago. For me, the largest risk, and this follows up on what Dr. Kotton mentioned earlier. But for me, the largest risk is of a false positive serologic assay that can lead to unnecessary lifelong therapy. And I've got to wonder, could this be mitigated by specifying that a single serologic assay alone should not be used as the sole basis for instituting therapy, whether we ask for repeated serologic testing or, my preference, viral load testing before the institution of therapy. So that would be my suggestion to mitigate that risk.

Dr. Wentzensen: Sorry. Can I ask you directly what the current clinical recommendation is? Because even with a Class III device, isn't there some recommendation for repeat testing, or is it really, as you described, a single test and then therapy?

Dr. Van Del Pol: Is there a recommended testing algorithm? Do you have information about that? There is for HIV.

Dr. Beavis: Yeah. Kathleen Beavis, University of Chicago. I just know that our practice is to follow-up with a viral load.

Dr. Van Der Pol: Does anybody recall whether CDC has an algorithm? Dr. Petti, you're raising your finger, so maybe I'll call on you and see if you have information about that.

Dr. Moore: I don't --

Dr. Petti: I'll let Dr. Moore first, and then I'll follow since we're here.

Dr. Moore: Sorry to jump in. No, there are definitely --

Dr. Van Der Pol: Don't forget to introduce yourself, please.

Dr. Moore: Sorry. This is Dr. Moore, University of Kansas, Wichita, Kansas. So there are algorithms that are published by the societies, and the hepatologists, the gastroenterologists, the infectious disease physicians, we all tend to follow those guidelines. I'm not aware of any clinicians that are prescribing lifelong antivirals for hepatitis B without the input of these specialists like us, but certainly that's just my experience in my community. CDC, I'm not aware of any specific CDC guidelines, specific CDC protocols or algorithms with regard to this, but there are recommendations that are made. Anyway, that's all. Thank you.

Dr. Van Der Pol: Thank you. Dr. Petti.

Dr. Petti: Yes, and, Dr. Beavis, I completely agree.

Dr. Van Der Pol: Don't forget to introduce yourself for the transcription.

Dr. Petti: Hi. Cathy Petti, Health Spring Global. Dr. Beavis, I completely agree with you that a single test does put high risk because the test results have extremely high consequences, and I would like to reiterate while we think about declassifying, down classifying, this to Class II, the particular wording and product labeling as an aid in the diagnosis, I feel very strongly verbiage like that should remain when we consider Class II device. As a clinician as well, we use a constellation of various different laboratory tests, including ALT, when we decide whether or not to treat or observe. Secondly, in the analytical validation, when we're talking about special controls, I know a lot of us in the laboratory industry feel pretty strongly that rigorous validation requires a pretty high end.

And if we can maybe set thresholds or guidelines on the tests needed to be run to meet these sensitivity and specificity thresholds, agree with Dr. Procop, I don't think that's negotiable, needs to remain very, very high, but at what end? And I think we've all seen that the more we test, it's a much more regular, rigorous, analytical validation. And, finally, I don't want us to lose sight of the fact that hepatitis B has international standards. So we're talking about an analyte that does have international standards, which makes, particularly among manufacturers, test performance being more harmonized, and for clinicians to be able to rely on these test results that is interoperable or portable across various different testing institutions. Thanks.

Dr. Van Der Pol: Thanks, Dr. Petti. Brad?

Mr. Spring: Hi. Brad Spring with Roche Diagnostics. A follow on to Dr. Petti's comments. I more or less want to make a statement and an ask. I've been around a while with diagnostics and seen many down classifications, and I don't recall any that have been down-classified where the performance standard has been lowered. The only time I've seen it change is in an up-classification that was with the flu tests that many of you may have remembered that the performance didn't

need to meet a higher threshold. So completely agree that the performance threshold should not change, but Dr. Petti mentioned this too.

I think some of the barriers of market entry are around the levels of evidence needed to establish that level of performance. And while I'm not necessarily asking for significant reduction in the amount of testing, it's really around considering alternative types of evidence when we look at testing. Because prospective trials are probably the most burdensome approach to establishing evidence, mostly because of finding the right type of patient and the right type of specimen. So, I would encourage the agency, as we look at this approach of special controls, to look at real world evidence standards, which I think is something we've been talking about a lot in the industry. Are there specimen banks we can leverage that are trusted? Are there other types of evidence we can use to establish that type of performance standard? Because I think that is one of the main barriers. And I think, Dr. Van Der Pol, you mentioned this too, one of the biggest changes we would see with a down-classification would be the reduction in the post-market, pre-approval, prior to implementation of any sort of change. But I would add, from an industry standpoint, that does not mean we change the testing that we do to then make a modification. We just would not require, for certain types of modifications, a pre-market clearance to do that.

Dr. Van Der Pol: Thanks. Dr. Caliendo.

Dr. Caliendo: Angie Caliendo, Brown. So I just want to reiterate the performance characteristics shouldn't change. Cathy made a very important point about "used in conjunction with." Several people have said that. The other thing that I was thinking might be helpful, since the goal here is to increase the number of tests that are available, increase access, so maybe instead of comparing it to one predicate, comparing it to two predicates when you're doing your studies. I'm envisioning a lot of different groups coming into this. And even though there is an international standard, is

that a way to mitigate variability from one commercial product to another? So I will just put that out as a potential special control.

Dr. Van Der Pol: Thank you. Dr Blumberg.

Dr. Blumberg: Emily Blumberg, University of Pennsylvania. One other area that I think needs to be addressed in terms of mitigation is it's my understanding that public health reporting goes through the labs that perform the test, not through the clinicians. And so you need to make sure we're talking about things like, for example, what Dr. Kotton was talking about with these false positive surface antigens, that there needs to be clear standards for public health reporting to make sure it's accurate for both characterizing disease and also avoiding unnecessary stigma for patients.

Dr. Van Der Pol: Agreed. Dr. Chiu.

Dr. Chiu: Hi. Yeah. Charles Chiu, UC San Francisco. I just wanted to make a point about the potential difference between qualitative and quantitative assays, because we're really considering a panel of four different assays. And, in my mind, serologic testing for, say, surface antibody, is quite different than HBV DNA. I mean, those are tests that are used for wildly different purposes. You would never order an HBV DNA, for instance, as a primary diagnostic test for hepatitis B. So there's certainly a risk, especially with the quantitative assays, of inappropriate use. If these are going to be used for screening, for instance, there's a potential risk that they're not being used appropriately. In addition, there's much more challenge with regards to standardization because these are quantitative assays. And based on, say, interpretation of viral loads, a response to therapy and viral loads, different tests can have widely different performance characteristics. They may not be linear. They may have different limits of detection. And so with regards to the molecular tests, which is the HBV DNA, I'm a little concerned about perhaps declassifying that. And the

question that I want to ask the FDA is, are we considering these tests as a whole, as an aggregate, or are we considering each test independently?

Dr. Van Der Pol: Dr. Stenzel. So when we sum up question number three, it's going to be sort of your recommendations, panel's recommendations, and I think the question for you just now is, do you want those recommendations by assay or as in aggregate as a group for HBV tests?

Dr. Stenzel: If there's specifics per assay, then I would provide them to us if there's specific concern. And I think there absolutely are differences between serology antigen and molecular tests. And there are different roles and purposes for diagnosis.

Dr. Van Der Pol: Okay. Mr. Spring and Dr. Chiu, if you're finished, if you'll lower your hands, or if you have a continue on question, leave them up. And, Dr. Karsner, you are next.

Dr. Karsner: Hi. Yes. Thank you. My name is Ryan Karsner. I am the Deputy Assistant Director for Hepatitis and General Viral Infections Branch in the Division of Microbiology Devices. I'm also an internist and infectious disease physician. I just had a couple points of clarification. One is, as we discussed, the intended use statements for all of these assays are as an aid in the diagnosis of hepatitis B. And we also have language in the labeling of these tests that the test results should be interpreted in the context of the clinical picture and other test results. And then the last point of clarification is that the CDC does have recommendations for interpretation of hepatitis B serologic test results. If you search for that, it'll be the first thing that comes up. It has a table with hepatitis B surface antigen, total anti-hepatitis B core and anti-hepatitis B service antigen antibody, and how to interpret those results. So there are recommendations that are published.

Dr. Van Der Pol: I would have been shocked if not. Dr. Garcia.

Dr. Garcia: Hi. Sure. Ines Garcia. I wanted to touch on Brad's point that there are alternatives to the clinical study. I mean, we are considering real world evidence. We also do consider retrospective samples as a way to supplement. Of course, where it gets very tricky is when you're

talking about like a clio wave type test with finger stick, which is a sample type that is much harder to store.

Dr. Van Der Pol: Very true. Dr. Caliendo.

Dr. Caliendo: Angie Caliendo, Brown. I just want to make a comment in response to Dr. Chiu's concerns about the quantitative DNA assays. Yes, they're quantitative, and they're more complex, but also the requirements are different. There's going to be an LOD requirement, an LOQ. There'll be linearity. There'll be reproducibility. And so what the FDA will require of a quantitative assay is different than what they'll require of a qualitative assay. And I think that as long as those performance characteristics are what they are now, we have a lot of experience with these assays. We know they work, that down-classifying them doesn't necessarily increase, in my opinion, doesn't increase the risk as long as we stick with those characteristics. And I think there are differences in LOD. There are differences in LOQ. And that's one of the reasons I said maybe more than one predicate device, right? So you can get an idea of how these compare across more than one test. But for me personally, that being a quantitative assay to me doesn't make me uncomfortable with down-classification, because I think the FDA has a lot of performance characteristics that are required to ensure how it functions.

Dr. Van Der Pol: Great. Dr. Pereira.

Dr. Pereira: Yes. Marcus Pereira from Columbia University. I think two points just, also in response to Dr. Chiu, I mean, the quantitative surface antibody test is often used for us to determine whether someone has responded to the vaccine or not based on certain thresholds. So hopefully that will also obviously stay the same in terms of its sort of test performance and quality. That's one minor point. The other sort of thought I had, in terms of risk mitigation, is when you order the panel of hepatitis B testing, the surface antibody, surface antigen, and core antibody, embedded in the results there is an interpretation, because obviously these are complex tests. And understanding

those, as one of the slides during the initial presentation included, you can have different interpretations about acute, chronic, isolated core antibody positives and so forth. So hopefully the downgrade wouldn't remove that sort of helpful interpretation. And I'm thinking more, not necessarily for specialists or those who use those tests often, and I think we generally have a facility in interpreting those, but if the idea is to increase testing and more and more providers who may or may not be that familiar with interpreting those tests are ordering them, it would be important to have some way or some help to help them interpret those complex tests.

Dr. Van Der Pol: Dr. Stenzel.

Dr. Stenzel: Yeah. I just want to reiterate that the standards we have for current Class III tests don't have to change necessarily for the down-classification to Class II. Standards can be the same. What we're really talking about is the amount of work required for the authorization. The time to authorization of a 510(k) case submission takes 90 FDA days, and PMA much longer, and the costs of the submission. All those do impact, potentially, the number of developers who invest in developing a test. But, again, the standards, you can make the recommendation, if you want, that the standard don't change going from Class II to Class III. Thank you.

Dr. Van Der Pol: Thank you. Dr. La Hoz.

Dr. La Hoz: I am reassured by both the comments of Dr. Ryan Karsner and Tim Stenzel that the comments, stipulations surrounding how to diagnose hepatitis B would not change with the potential reclassification. But maybe a comment on what Dr. Caliendo and Dr. Chiu have mentioned before about reclassifying all of them at the same time versus some of them is the possibility that those populations that don't have access to care may have all of the tests performed at the same time just to adequately categorize them as only core positive versus core plus antigen plus DNA plus LFT abnormalities plus abnormal INR. So if we were to just reclassify a few of

them and not all of them, we may end up with, again, a potential disadvantage to quickly diagnose them and, you know, assign them a certain degree of severity or priority to treat.

Dr. Van Der Pol: Thank you. Dr. Chiu, back to you.

Dr. Chiu: Yeah. I think Dr. La Hoz expressed it really well. This is my main concern. In my mind, if the reason for declassifying in the first place, the primary reason, is really to improve access to care, you would only really need to down-classify the serologic test. And then, you know, the quantitative serologic tests and the quantitative DNA tests, those are used once the patient's in the system. You want a patient being followed carefully by an expert if a patient really has the newly diagnosed hepatitis. And so why can't we selectively down-classify, for instance, the serologic test, ensure that the patients at least have screening and have access to care, and then get them into the system where you would send off all of these additional tests because there are more tests than just, you know, these hepatitis tests, the INR, liver function, et cetera. If your purpose is really for screening, then why do we need to down classify all of them at the same time? I think that's my question.

Dr. Van Der Pol: And I think I'm just going to reiterate that the purpose isn't just for screening, the purpose is to determine whether or not we have enough information to say that special controls are sufficient to get these products to market. And I would also just, from an STI perspective, there are now molecular tests that are available at the point of care. They're not all clio waves, so some still need laboratorians to run them, but I think that one of the things, when people are talking about access to care, is we have to remember not every person in the US lives in an urban center where they can go in. So just because you have follow-up tests at large urban health care centers doesn't mean that people all over the country do. And we are a leader in the world. And I think this has global impact. So I would just throw those things out for your

consideration. But I promise you, when we get to the next question, I will call out by different types of assays so that everybody has a chance to be heard again on that topic.

Dr. Petti.

Dr. Petti: Yes. Cathy Petti, Health Spring Global. I just will reiterate what you just said, Dr. Van Der Pol, that I think bringing it down to a Class II, the added benefit is increased access, but I strongly believe that we've had years of experience, and the technology has proven itself to be reproducible, accurate, and reliable. And for those reasons, we are data informed that Class II would allow us to deploy these tests in a safe and effective manner.

Dr. Van Der Pol: Nice summary. Thank you. Dr. Caliendo.

Dr. Caliendo: And I would just add that one of the points that the FDA made in our introduction on classification was that tests should be classified at the lowest level possible based on safety and efficacy. And so that's part of their mission too, right? What is the safest, based on safety and efficacy, what is the lowest level where they can, with special controls, down-classify?

Dr. Van Der Pol: Dr. Wentzensen.

Dr. Wentzensen: Yeah. I think there is some perception and probably experience among many of us that we have the PMA process, which is like extensive, elaborate, and can be a barrier but assures that the tests are properly evaluated. And then we have the less 510(k) process, which sometimes is viewed as okay, very minimal standards, and maybe concerning. But maybe can we hear some examples of special controls how you can move between these two extremes, and how you can make sure that the standards are truly not changing? Because I mean, there is a concern. I mean, there is a difference in the process, and that concern is probably what makes some of us hesitate a little more and, while wanting to lower the barrier, not risking any deterioration in test performance. So I think that it would be great to hear a little bit more what could be done, and how we could move somewhere in the middle ground.

Dr. Tim Stanzel: I can start, and then if any of my FDA colleagues want to add in. So, again, I'll just reiterate that you can make the recommendations that the standards for each type of hepatitis B device stay the same or equivalent to what it is right now. And we can certainly move forward with that, if that's the best thing to move forward with now and see how that works. There may be other mitigations, though, that allow, say, easier development of over-the-counter or point of care tests. And when you look at the benefit risks, it could be that a slight decrease in sensitivity or specificity is outweighed by the fact that there is a lot more access to testing. As we saw with the pandemic, access to testing at home was really important to help the spread of disease, and that's really what we're trying to get at here.

Can we eliminate the spread of hepatitis B? Can we limit and mitigate the morbidity and mentality from Hepatitis B? Can we make diagnoses more early in infection? Can we prevent vertical transmission? All these things are huge benefits. And when you look at benefit risk calculations, and we can model this and are open to modeling this, when you have measured performance differences, though slight, between, say, a point of care or over-the-counter test and the increased access to testing, we can also mitigate by -- it says my Internet is unstable, so hopefully you can hear still hear me -- we can mitigate through labeling. So this might be, you know, you need to go see your clinician, and you need repeat testing, things like that. Special controls aren't just writing in necessarily exactly what's, say, in a PMA product right now, but we can add for certain situations. We can add additional mitigations through the down-classification process.

I see my colleagues, Ines or Uwe, might have something to add as well. Thank you.

Dr. Garcia: Hi. Ines Garcia. Yes. I wanted to build on that. So, the special controls do have some built in flexibilities in case there are alternate approaches that come up. They are generally written to describe the types of studies that we would expect to see, for example, like cross

reactivity, precision, you know, the analytical studies. In general, they may describe a clinical study or method comparison study to give you an idea. Also, there could be labeling mitigations, such as limitations that need to be added and other special considerations with specific environments in which the testing should be performed or any kind of instructions for the training of the test operators. So to give you an idea of what some of the special controls may look like.

Dr. Wentzensen: So can I, just to clarify, you could, in theory, have a special control that asks for a PMA like trial or trial data, but it's still like a Class II approach. Is that correct?

Dr. Garcia: Exactly. You got it right.

Dr. Van Der Pol: Dr. Scherf.

Dr. Scherf: Yeah. Dr. Uwe Scherf. Just to add to Tim's and Ines's description here, , it's correct. So to make a point here for HBV, is also something, I think, that we would like to share. I mean, we have been reviewing these products for 12 years. They have been out in the market, and I think it has been mentioned earlier that they have established their performance and their use in the market. When we now think about down-classifying, it doesn't mean that, first of all, we need to remove or decrease the performance. We do not need to remove any evaluation approaches like WHO standards. We will not do that because this gives us, even in the PMA environment, the assurance it's safe and effective, and there is no need for us to move away from that because it's part of the evaluation. That will also happen in the 510(k) paradigm. Now, it was mentioned by our NCI colleague that 510(k)s are maybe less strictly evaluated. I would not necessarily stand to that word. Yes, they are different, differently evaluated, but to a level that at the end of the day, FDA and our medical colleagues can determine they are safe and effective, and they are willing to use them.

Dr. Van Der Pol: Dr. Pereira.

Dr. Pereira: Yeah. Marcus Pereira of Columbia University. I'm going to bring up something that I don't, I apologize to my colleagues. I don't have my thoughts fully together, but I guess a question about reflex testing, which we do have for confirmatory testing, for example, for the diagnosis of HIV. And sometimes when there is a sort of indeterminate result or even sort of as a standard, and we don't have that in hepatitis B. And obviously it's a much more complex situation with different sort of states of infection or non-infection, but is that something that in the appropriate situation, which would have to sort of fully outline, is that something of a possible special control in certain circumstances?

Dr. Stanzel: Tim Stanzel, FDA, yes. We could put that in as a special control for new settings of testing, for example.

Dr. Van Der Pol: Dr. La Hoz.

Dr. La Hoz: This is Ricardo La Hoz from UT Southwestern. I think that what I am hearing from our colleagues from FDA is that the hepatitis B tests have been evaluated for over a decade with a good diagnostic performance. We've also heard that there's a fair amount of safeguards to ensure the performance, that the performance of the tests, if they are reclassified, will remain the same with a high sensitivity and high specificity. We've also heard that we can keep the same statements regarding the complexity of diagnosing hepatitis B with regards of putting the test results in the context of many other things that, I assume, they're well stipulated in the Class III classification. So to me, if we have all these safeguards, the predominant pro is really increasing diagnosis at multiple levels, which is preventing vertical transmission, preventing transmissions amongst populations that currently have a high prevalence of the disease. So, to me, I'm hearing that there's a fair amount of safeguards in place, and the big pro is improving access overall. One comment that was made was which information will be provided for those seeking approval for a Class II. I think if we make the bar so high that it is similar to a PMA, without necessarily being a PMA, we

may defeat the whole purpose of what we are trying to achieve. So the safeguards need to be there. No doubt. But the safeguards need to be enough that they provide us with the reassurance that they will perform correctly, avoiding the risk, but not high enough that again, it eliminates the increase in excess.

Dr. Van Der Pol: That's some great points there. I mean, I think that gets us kind of into considering what is the absolute minimum sensitivity and specificity. If you're going to put special controls in place, what do those need to look like? And we've heard from several people that they have to be exactly where we are right now, which is 98, 99. Is that what we really need to provide safe and effective, good quality tests? Again, recognizing that every test not done is a failed test. So you know, maybe those special controls need to be considered, but I don't think that's really the purview of this panel. So, I'll move this on and let Dr. Ng get in her two-cents worth.

Dr. Ng: Thank you. Valerie Ng, Alameda Health System. I wanted to bring up the issue of harmonization. If we move it from just a few manufacturers today to many more, I do know my current assay, CIFU, clearly states you cannot mix and match results from different manufacturers. So then that gets to, specifically, issues like the qualitative and the quantitative surface antibody test. Are we going to pay the interpretation at 10, at 12, whatever the units are measured? Are we going to have one being more analytically sensitive than the other? And then how do we interpret that? And then I want to talk about the surface antigen. My current assay involves an initial positive must be tested in duplicate, and then must undergo a neutralization. How are we going to assure other formulations of surface antigen tests have the exact confirmation, so we are not managing a series of false positives, which is why I think I have this whole reflex testing program for that particular test?

Dr. Van Der Pol: And we're going to come to that with question 4, because that's a valid point. Dr. Petti.

Dr. Petti: Cathy Petti, Health Spring Global. I just wanted to clarify an earlier comment I had made about special controls and the sample size calculation and power calculations in the "N." The "N" I meant was demographics. I know the FDA does this, but would like to emphasize again that we have the appropriate patient populations represented, the vaccinated, the unvaccinated, those at high risk, and those at lower risk. I think that would be very, very impactful in better understanding test performance.

Dr. Van Der Pol: Agreed. Dr. Stenzel.

Dr. Stenzel: Yeah. I'll first respond to Dr. Petti. Yes, we like the diversity of the patient population, and we have a new diversity enhancement policy that we really want to include patients from all different groups as well. I also wanted to respond to an earlier comment, and I forget who it was. It might have been Dr. Wentzensen about if we make the bar for performance as high as it is -- I think it was Dr. La Hoz -- for PMA, and then you're going to try to get point of care or over-the-counter tests, that could be incredibly valuable. It can definitely act as a disincentive to develop. We have potentially seen this with hepatitis C. Even though we have down-classified it, we have not seen a tremendous upswing in submissions. And we essentially matched in the special controls for the down-classification of hepatitis C, the performance expectation that we saw in PMAs. And we do have some feedback that may be inhibiting innovation here and the ability to access testing for hepatitis C. So that is something certainly the panel should consider here is ultimately what is the goal in hepatitis B testing? How can classifications of the device impact reaching the public health goals of hepatitis B testing? Thank you.

Dr. Van Der Pol: Dr. Wentzensen.

Dr. Wentzensen: You know, I fully agree with your statement, but I think it goes back to the fact that there are different indications and different types of tests. And I think for like a point of care test that can extend coverage of the test, like accepting a slightly lower performance would

be, would be a great trade off. But for other tests that we're discussing, we may not want that. So I think that it sounds like that is achievable through a Class II process through the special controls. And I think that is, to me, that is a really very reassuring message to hear about moving in that direction.

Dr. Van Der Pol: And I think that's one of the areas where mitigation via labeling helps us, right? So we can actually say this test has somewhat lower sensitivity, so you must do a confirmatory test or some sort of reflex test, which we've discussed. Dr. Procop.

Dr. Procop: Well, you just stole what I was going to say.

Dr. Van Der Pol: Sorry.

Dr. Procop: So I get the idea of potentially lowering, say, sensitivity specificity in order to increase access. I will also say erroneous test results cause harm. So that's something to consider too. So we're going to really have to walk that tightrope. And I think that tightrope really is mitigated if, if you lower, you have to impose a diagnostic algorithm that will right the wrong.

Dr. Van Der Pol: Couldn't agree more. Has everyone gotten everything off their chest that they wanted to share? I'll try to summarize it unless I see another hand or two. Dr. Moore.

Dr. Moore: Just one thing. I basically spend all day seeing patients, and I get a lot of calls about false positive hep B core IGN testing, which is problematic. I was just going to say that, from my perspective, I think if we have increased access to care by making, inviting product developers to bring assays to the market by downgrading it to level II, from my perspective, I think that would be the best option. But that would be the qualitative testing, the serologic testing. But the quantitative testing, either bringing it down to level II and having a special control on it or leaving it to level III, that, to me, is the most critical aspect because you really don't want to have false negative. I know that downgrading level II doesn't imply a reduction in specificity or sensitivity,

but there is a possibility that may happen. I think we need to leave that at level III or level II very significant special control.

Dr. Van Der Pol: Okay. Thank you. Dr. Stenzel.

Dr. Stenzel: Yeah, and thank you, Dr. Moore. Tim Stenzel. Yeah, definitely we can have more or less flexibility around different technologies, as we don't. That's fine. And it may be that those technologies that are largely used to confirm or provide additional information after diagnosis or confirmation of diagnosis can remain at a higher bar than something that would allow point of care or over-the-counter testing. Thank you.

Dr. Van Der Pol: And this is a place probably at which we consider, you know, different controls for screening versus diagnostics, right? We don't always disentangle those, but we often should. And I think maybe this is one of the places where that would be appropriate.

Okay. So I'm going to sum this up. What I'm hearing is that, in general, the panel believes that there are mitigations that should be put in place. Those mitigations include labeling about when it's appropriate to use. Maybe we say things like these tests aren't appropriate to use within a month of vaccination, for example, but labeling mitigations; intended use mitigations that cover what clinics or what circumstances testing is being done; maybe disentangling diagnostics from screening; requiring follow-up testing was something that we heard fairly often or confirmatory testing; and that labeling must include language such as an aid in diagnosing, again, suggesting that further testing may be necessary, but also that the interpretation has to be embedded within the clinical context. And so then we've talked about also those special controls, including the sensitivity and specificity, to either remain where they are with the assays that we currently have available that originally achieved approval using the Class III process, whether we need to stay at those same levels of sensitivity and specificity, but, regardless, there do need to be very carefully considered special controls there. And that qualitative and quantitative assays may actually have

different needs in their labeling and mitigations. We also had concerns, as I just mentioned, to make sure that we differentiate between some of these different needs and that it's not one blanket set of mitigations, but it may have to be assay specific or type of assay or area of use of assay, so point of care versus laboratory-based testing.

So, Dr. Stenzel, is this adequate, or did you have further questions on the topic of mitigation? You're muted still.

Dr. Stenzel: Apologies. Tim Stenzel. Yeah. I'm satisfied, but I want to give my colleagues at the FDA who are on the line, it looks like no one else has anything to add. So thank you so much for this.

Dr. Van Der Pol: Yes. It was a really robust discussion, which I think is very helpful, and I appreciate the different perspectives that everybody's bringing to the table. So let's go on to question 3.

Question Three

Dr. Van Der Pol: And I will remind you, so this conversation is based on the information presented here. Discuss whether or not, based on the available information, the panel believes the FDA should initiate the reclassification process from Class III to Class II. Again, I will remind you that we can contextualize that by different types of assays, so antibody assays, antigen assays, molecular assays, qualitative, and quantitative, however the panel feels that that's appropriate. I would also remind you of the information that we were given in the very first presentation from the FDA that we are really supposed to help the FDA make the decision about whether or not there's enough information available and enough data available to inform creating special controls because, if there is that level of information, then it would be appropriate to move to Class II, that many things come at Class III while that information is lacking. So with that in the back of our minds, I'll open it up for conversation about whether the panel believes that the FDA should start

that process of down classifying HBV tests. And you can put that in terms of whatever assay you want to focus on.

Dr. Blumberg.

Dr. Blumberg: I'm going to vote or speak in favor of --

Dr. Van Der Pol: I'm going to just remind you that we're not voting.

Dr. Blumberg: Oh, sorry. Yes.

Dr. Van Der Pol: So just to make sure that we're clear, and we don't cross any boundaries that we're not supposed to cross.

Dr. Blumberg: Thank you.

Dr. Van Der Pol: That said, I'm sorry. Please go ahead.

Dr. Blumberg: Emily Blumberg, University of Pennsylvania. I think it's time to consider a stepwise reclassification of these tests, specifically screening tests that may be used to improve access to diagnosis. I do not think these tests should necessarily be ones that will be used to determine treatment, but rather to identify at-risk populations, and so would focus on that specifically to improve access, but ensure that adequate safeguards are in place so that people do not then see these as final results, but really an entry into health care.

Dr. Van Der Pol: Can I ask you a follow-up question to make sure that we get back to this? And do you feel like there is insufficient data to allow us to create special controls and mitigations for diagnostic tests?

Dr. Blumberg: You mean for, I guess I'm concerned about interpretive, you know, providing adequate guidance for interpretation specifically to guide treatment. So I'm a little less comfortable with that.

Dr. Van Der Pol: So you think there aren't data based on the class --

Dr. Blumberg: I think there is insufficient data, to me.

Dr. Van Der Pol: Okay. That's fine. I just want to make sure I'm clarifying that. Dr. Procop?

Dr. Procop: Yeah. I'm supportive of moving these to a Class II. I think there is sufficient data. I'm going to echo Dr. Petti from earlier. We've been doing these tests for a long time, and so I think if we look at that data, the FDA will be able to put in sufficient safeguards for both types of test screening, as well as molecular diagnostics.

Dr. Van Der Pol: Thank you. Dr. La Hoz.

Dr. La Hoz: Hi. This is Ricardo La Hoz from UT Southwestern. I think the tests have a great track record with great performance, diagnostic performance. The safeguards can be placed. Comments can be made about how to interpret the tests. I think that a proportion of patients that may be infected with hepatitis B may not have access to confirmatory testing, and I think that can also delay initiation of therapy. So to me, if the diagnostic performance can be kept, I think the benefit is there. Everything in medicine is a pro and a con. So initiating therapy in rural areas where patients may not be able to drive to somewhere where there's confirmatory test is something to consider. So why not keep the same diagnostic performance and proceed with the classification and use them as the Class III are currently being used. It's an important consideration. I think the possibility of misclassification of the results will continue, even if we keep them Class III, and that is an issue that also needs to be considered. While I think that reclassifying them can potentially improve the access to care and the net benefit be more significant, those errors are going to continue despite the reclassification approach.

Dr. Van Der Pol: Thank you. Dr. Caliendo.

Dr. Caliendo: Angie Caliendo, Brown. I am comfortable down classifying all four categories of tests. I think we have adequate information and experience, and we've discussed appropriate special controls.

Dr. Van Der Pol: Thank you. Dr. Beavis.

Dr. Beavis: Kathleen Beavis, University of Chicago. Ditto what Dr. Caliendo just said. And, as a pathologist, I've seen the evolution of these tests over the last 25, even 30 years, and they're so close. They've just gotten so much better that I'm very confident that there is information available to the FDA to be able to down classify these and put on the special controls.

Dr. Van Der Pol: Thank you. Ms. Schwartzott.

Ms. Schwartzott: I do agree that we should be moving towards Class II designations. I, as a patient, I'm thinking about my population. And I do not have hepatitis myself, but I do have liver disease. And I'm lucky that I'm okay, but others are not. What we really should be thinking about is the people that aren't getting diagnosed and that are going to develop all these higher-level stages of liver disease because of lack of diagnosis. And there are no, very few treatments for people with liver disease. Not everybody's going to qualify for a transplant. There are very few medications, and a lot of these people end up dying from this. That's what the real risk is. If they're not diagnosed, if they don't receive early treatment, this is what's going to happen. As for all these tests that are currently out, the risks are very low. I think labeling is key. I think it needs to be clear, not just for the medical community, but if somebody is taking home one of these tests from their pharmacy, they should have specific and clear labeling. But the important thing is to get these out to the general public, to the people that can't get the care that I can get, that we can get on this panel. And so whatever is the easiest mechanism that's safe and effective should be available.

Dr. Van Der Pol: Thank you. Dr. Pereira.

Dr. Pereira: Marcus Pereira, Columbia University. I agree with Dr. Caliendo and Dr. La Hoz. I would support the reclassification of all of these devices to Class II provided that those parameters, in terms of test performance, maintain a high level, such as what they are currently stated at. I agree what Dr. La Hoz says that the misinterpretation of these results is currently happening, and switching it to Class II probably will not deteriorate that interpretation, in fact, actually by

instituting special controls, in particular when it comes to labeling, and making sure that either the providers or even patients themselves are given the information necessary how to appropriately interpret and take the next steps with these tests, actually might enhance interpretation. Obviously, that would have to be carefully worded, but there is a potential here for actual improvement. Obviously, the underlying concept here is that improved access is a greater benefit than any of the risks for these tests.

Dr. Van Der Pol: Thank you. Mr. Spring. Oh, I lost Mr. Spring. Sorry.

Mr. Spring: Yeah. I clicked it twice. I also support the down classification. I think going to Class II will increase patient access, but probably just as importantly will help the continuous improvement of those tests that are currently on the market today. And then one final comment. I know we're talking about US patient populations, but global regulators do follow and closely watch FDA's lead in these areas, and I think it will encourage future down classifications and other countries around the world and increase access there as well.

Dr. Van Der Pol: Dr. Petti.

Dr. Petti: I also support the recommendation to reclassify Class II for all the assays listed with special controls.

Dr. Van Der Pol: Thank you. Is there anyone we haven't heard from? Dr. Wentzensen.

Dr. Wentzensen: I concur. If it was not clear before, I just wanted to be very clear that I agree with the direction.

Dr. Van Der Pol: Dr. Kotton.

Dr. Kotton: I also just want to give my support for downgrading. Thank you.

Dr. Van Der Pol: Dr. Walker.

Dr. Walker: Dr. Walker. I also concur with the discussion and the agreement to downgrade to classification II.

Dr. Van Der Pol: Dr. Chiu, did we hear from you?

Dr. Chiu: Yeah. No. I concur with everyone else about downgrading to II, as long as, as we've discussed, the special controls are implemented and they're assay specific, especially my remaining concern is still with the quantitative assays. But as long as there are appropriate special controls in place, I'm in favor of downgrading all four.

Dr. Van Der Pol: Dr. Moore, did we hear from you? And Dr. Moore gives us a visual thumbs up, which I'm going to put into the record verbally.

Dr. Moore: All I can say is I concur with the discussion. I have nothing to add.

Dr. Van Der Pol: Okay. Have I missed anyone?

Dr. Ng: My hand is up.

Dr. Van Der Pol: Oh, sorry. Dr. Ng.

Dr. Ng: Yes. I just want to say the answer is yes.

Dr. Van Der Pol: Okay. Anyone else? Okay.

I think I can summarize this one for you, Dr. Stenzel, pretty quickly. The panel in general believes that it would be appropriate, based on the amount of data that we currently have about how these tests perform, to consider starting the process to downgrade them to Class II. The panel is not concerned but is adamant that the special controls do need to be in place that dictate the high level of sensitivity and specificity and also that special controls will need to be in place to mitigate any potential risks of using these in certain patient populations, for example, those who have been recently vaccinated, and to distinguish perhaps between diagnostics and screening, and that, for quantitative assays, there are special controls that cover limited detection, limited quantification, and linearity so that we know exactly what these results mean. And I think that's the overall consensus of the group. I didn't hear any that had strong feelings against starting the process of down-classification. Did you have any other information that you were looking for from the panel?

Dr. Stanzel: I think we got what we need. I want to really thank the panel on this analyte, and we take seriously the charge to make sure that special controls in the down-classification process are carefully worded and take into account patient safety. Thank you.

Dr. Van Der Pol: Excellent. There is one remaining question before lunch, so don't get your hopes up too quickly. So let's look at question four that I think people were concerned about along the way.

Question Four

Dr. Van Der Pol: So currently there's no authorized tests for detection of and quantitation of surface antigen for HBV. So would you please discuss what you would think the appropriate intended use for such a device would be? Discuss potential risk for both detection and quantitation of hepatitis B surface antigen and whether or not you think there's enough data that we could build special controls and put measures in place that would mitigate risks to health.

So, if I could have input from the panel, I know that some people have already been talking about quantitation, and one of the questions that was already raised is whether that quantitation would be similar across all assays so that we would have some consistency of the meaning and interpretation of those quantitative values. I think that was one of the ones that was raised.

Dr. Ng.

Dr. Ng: Thank you. I think I would like to restate that. Quantification for me, for a meaningful result, would not be with surface antigen. It would be with a NAT test. I'd want to know a viral load because that's what I would monitor the effectiveness of treatment. I think the question I would want answered, if we are going to work on quantification assays, is what is the relationship of an antigen assay to a NAT? I would want to know if I pick it up on an antigen assay, would I always have a measurable viral load? And then I would want to know how to interpret it

when there's a discrepancy. And finally, buried in all of that, is how did these antigen assays perform with the various variants?

Dr. Van Der Pol: Great questions. Dr. Moore.

Dr. Moore: Yeah. Dr. Moore at University of Kansas. I apologize for this simple semantic question. Can I ask for clarification? Are we talking about two separate or a single test that is detection and quantitation or detection and then also quantitation?

Dr. Van Der Pol: Yes, the 2nd. So potentially two separate assays or one assay at the same time. I mean, it could go either way, but don't think they have to be bundled.

Dr. Moore: I understand. Okay. Well, with that said, I agree with the previous comment that the quantitation of hepatitis B surface antigen is not useful to me clinically. The PCR based DNA quantitation is really the best, and really just the presence or absence of the hepatitis B surface antigen is all I'm really interested in.

Dr. Van Der Pol: So you would like a qualitative assay only? So yes, no?

Dr. Moore: Yes.

Dr. Van Der Pol: And one of the parts of this question, this was a complex question. I'll just remind you that one of the parts were what would the intended use for such a device be? And since you've said that this might be of use to you, what would the intended use be, and what are the potential risks of an assay such as this?

Dr. Moore: Well, the use would be as a screening tool to clarify who has active infection, who doesn't. And then from there, use that as a springboard to then launch to the hepatitis B PCR. So, to me, it would be used as a panel as part of a serologic test, screening test, and there I think it would be beneficial to have just to extend the discussion further, make it as accessible as possible within limitations, obviously, with regard to the qualitative aspects. I mean, the screening tool.

Dr. Van Der Pol: And as long as we're still on you, are there any specific risks to this test that you would like to mention that need to be mitigated?

Dr. Moore: Right. Well, the risk is just having a false positive, and then you'd have to have some caveat that states that confirmatory testing is recommended. Although, you know, honestly, the performance characteristics of the tests to date are pretty darn good, and false positives are quite rare.

Dr. Van Der Pol: Dr. Caliendo.

Dr. Caliendo: Dr. Caliendo, Brown. You know, it's kind of interesting. Could this test be an inexpensive version of a NAT? I don't know the answer to that, and that's what I would like to know. And I think Dr. Ng was kind of bringing that up. How does this relate to NAT? Could you use it as a, if it's negative, it's useful because you've treated below? Could you use it as an inexpensive NAT? You'd need to know its LOD and how that compares to nucleic acid testing. I don't know if there's an international standard for hep B antigen. So I'm not thinking about it so much as for screening. I'm thinking more of it as an inexpensive alternative. There are risks, right? In that situation, if it's not adequately sensitive, it's a problem. Because that's my own experience. This was hepatitis C antigen that never got sensitive enough. I think the correlate was 10,000 before you got a positive antigen, so clinically it wasn't useful. And so, to me, that's kind of one way to think of the test, could be useful if it actually worked, but I don't know that there's enough information to know if it could actually work as a substitute.

Dr. Van Der Pol: And I know Dr. Stenzel needs to pop in, but I want to ask you a clarifying question before we leave you, Dr. Caliendo. Are you saying that you would see this as a tool for monitoring people on therapy?

Dr. Caliendo: Potentially. I don't have enough information to answer that, but I'm seeing it that way. Potentially. Yes.

Dr. Van Der Pol: Okay. Dr. Stenzel.

Dr. Stenzel: Yes. Thank you. I'm following Dr. Moore's comments. I just wanted to clarify the role of the FDA, at least in CDRH, the device center, and submission. So we, only in narrow circumstances, consider clinical utility. That usually is combination devices like a companion diagnostic, but for something like this we look at is it safe and effective either as screening or diagnostics. So there is nothing preventing somebody from developing a quantitative surface antigen test and submitting it to the FDA. It's just a question whether it would be a Class III submission or a Class II submission. And as long as it's safe and effective in either classification, then we could move forward to authorize it. But we largely stay out of the practice of medicine and clinical utility. That's something that insurance companies and payers consider, but largely not the idea for these kinds of devices.

Dr. Van Der Pol: And Dr. Garcia. I'm trying to let the FDA go in response to previous before we move on to other panelists.

Dr. Garcia: Sure. To answer Angie's question, there is a surface antigen international standard. And I know there's been a lot of questions in the field and also among manufacturers, like how is this test going to be used? And why is that question coming up? Because that's going to drive what the clinical study is going to look like and what the intended uses are going to be, which is why we're looking for your thoughts on the quantitative surface antigen tests.

Dr. Van Der Pol: Dr. La Hoz.

Dr. La Hoz: Hi. This is Ricardo La Hoz from UT Southwestern. I think there are two potential uses, but the most important message I would like to send is that I think we need more information. But the first one is the hepatitis B surface antigen mutants and occult hepatitis B where there may be a lower production of hepatitis B surface antigen, and how can we use the quantitative assay to better classify those two scenarios versus a surrogate marker of treatment response, as it's been

alluded by Dr. Caliendo. But I am unaware of information to really help us guide in that regard. So I don't think we have all the information.

Dr. Van Der Pol: Thank you. Dr. Blumberg.

Dr. Blumberg: Emily Blumberg, University of Pennsylvania. At the risk of repeating what other people have said, I would just say that based on the comments that have been made, many of which I've been thinking about as well, I really don't think we have sufficient information at this point to move this forward in the same way as the other tests. There are many circumstances where you could imagine it may ultimately be helpful, but practical use of this now is insufficient to move it forward. I think more data is definitely needed.

Dr. Van Der Pol: Dr. Petti.

Dr. Petti: Cathy Petti, Health Spring Global. To follow up Dr Garcia's comment, with respect to the international standard, and to follow on Dr. La Hoz's comment, I know we do have that international standard. We also know that there is tremendous variability in genotypes in many using these international standards for surface antigen. So I do encourage us to explore this type of assay, because I think it may be a useful tool in our armamentarium for hepatitis B treatment and decisions for treatment that I think we do not have enough information. I think it's very important for us to maybe support organizations that want to gather information in this area and, in particular, pay attention to testing variability with the genotypes like we've seen with our other hepatitis viruses.

Dr. Van Der Pol: Thank you. Dr. Kotton.

Dr. Kotton: So I was wondering if anyone on the call had expertise regarding whether or not NAT testing misses certain variants, and I know that sometimes surface antigen, there can be a gap where surface antigen is negative and nucleic acid testing is positive. But are there instances where,

due to mutations, nucleic acid testing doesn't pick up certain variants, such that we would really want a really useful surface antigen. Does anyone know of that situation?

Dr. Van Der Pol: Dr. Garcia?

Dr. Garcia: Sure. Yeah. So we haven't seen any evidence to that effect that our tests are missing certain variants. That's not to say that that doesn't exist.

Dr. Kotton: Okay. I know it's an issue for some of the other nucleic acid tests that are out there, not for hepatitis B, but outside of hepatitis B. But I haven't really heard of it here. So as long as it's not a major issue, then that doesn't seem like we need surface antigen for sort of backup testing the way we do use NAT testing for backup testing when surface antigen is negative, but we have a concern for active disease. Thank you.

Dr. Garcia: Yeah. And to build on your point, there is, of course, the concern with the surface antigen and its detection of the different variants. And as Dr. Petti mentioned, you know, the differences with the genotype detection, so that could definitely be an issue for the surface antigen tests that we would need to find a way to mitigate.

Dr. Van Der Pol: Dr. Chiu.

Dr. Chiu: Yeah. Maybe I can just start by addressing kind of Dr. Kotton's comments. So the hepatitis B genome has extremely low diversity, and the primers have been developed essentially. To my knowledge, I don't think there have really been mutations that have been identified among the sequence world, the genomes worldwide for hepatitis B. And so as a DNA virus, it has extremely low diversity. So I'd be much less worried about potential escape from detection by nucleic acid test, versus to an RNA virus such as HIV or hepatitis C. But that being said, I agree with the rest of the group. I feel that this particular test, the quantitative hepatitis B surface antigen, it's still looking for an indication. I mean, there have been some promising indications that might be useful for evaluating response to therapy in parallel with hepatitis B DNA. I think right now we

don't know whether this particular test has any advantage over simply running HBV DNA beyond the fact that it might be an easier test to run or a lower cost test. So I agree with the rest of the group that I feel that there's not enough information to downgrade or down-classify from Class III to Class II for this particular test.

Dr. Van Der Pol: Dr. Ng.

Dr. Ng: Yeah. I just wanted to add to why I want to know the relationship, because you got that pesky problem of those empty variants, right, like 100 to 1 ratio? And so how does that play out as an antigen test versus a NAT? I think I go with the NAT. That's my sense.

Dr. Van Der Pol: I'm going to throw in one more question for the panel before we try to wrap this up, because we're hearing a lot of the same thing that there's not enough information and that we don't know how this would be utilized or where it would be adopted. And those are all fine questions, but I want to just kind of restructure. The question is do we have enough information to say what the special controls would need to be or what the labeling would need to be if such a product were developed? So, whether or not it should be developed is kind of a different question, and it may be not. But if somebody wanted to develop it, do we have enough information to say that based on that decision tree that we have enough information that we can actually develop special controls for a test like this? So, it should be put into Class II from the get-go? Or do we not have enough information about what the risks are that we need to mitigate using those special controls and so it needs to be started at Class III? I think that's a question I'd like to hear the panelists sort of address.

Dr. La Hoz.

Dr. La Hoz: This is Ricardo La Hoz from UT Southwestern. I'm unaware of enough information to say that we can have special controls to classify.

Dr. Van Der Pol: Thank you. Anyone else? I'm seeing many people shaking, nodding their heads. So I assume this is a consistent response from the panel. Does anybody want to add anything, or shall I try to summarize? Seeing no hands, I'll try to summarize.

So, Dr. Stenzel, with regard to question 4 about whether or not a surface antigen qualitative or quantitative test should be Class III or Class II, the panel doesn't feel like there's sufficient information to help develop special controls. So at this time, we don't have enough information to support moving this to Class II. So if someone does present data to the FDA about a test such as this, it should be evaluated under a Class III mechanism, according to the information that we have available to us at this time.

Can I see nods? I think that that was a pretty united consensus. Does that give you the information that you need, Dr. Stenzel, or do you have additional questions?

Dr. Stenzel: Yes, it does. And we thank the panel, and we just wanted to be complete in our questions. And we understand that this is the panel's opinion as of today with the information we have today. Thank you.

Dr. Van Der Pol: Okay. We are nearly perfectly on time. We have one presentation that was scheduled for before lunch from the FDA, but we're going to move that back and let everybody take a break because we've had some really good, strong, robust discussions. And so, we'll take our lunch break now, and we will come back on the hour. So we will see you in an hour and four minutes. Thank you, everyone.

Background of *Mycobacterium tuberculosis* Assays

Dr. Van Der Pol: Welcome back. It's now 1:00 Eastern time, and I would like to resume the panel meeting. We're going to invite the FDA to start the next presentation. I would like to remind public observers at the meeting that while the meeting is open for public observation, public

attendees may not participate except at the specific request of the panel chair. FDA, you may now begin your presentation.

Dr. Karsner: Hello. My name is Ryan Karsner. I'm an infectious disease physician and the Deputy Assistant Director for Hepatitis and General Viral Infections branch within the Division of Microbiology Devices. This presentation will discuss the potential reclassification of qualitative serology-based Parvovirus B19 antibody in vitro diagnostic devices from Class III to Class II with special controls. The purpose of this panel session is for the panel to discuss the potential future reclassification of Parvovirus antibody assays.

FDA is ultimately seeking recommendations from the panel members and the public on whether sufficient information exists such that the development of special controls, which along with general controls, could mitigate the risks from these devices such that the devices would provide a reasonable assurance of safety and effectiveness and, therefore, can be eligible for a Class II designation. The intended uses for these Parvovirus antibody assays are for the detection of IgM antibodies and IgG antibodies as evidence of Parvovirus B19 infection and may be used as an aid in the diagnosis of past or current infection with Parvovirus B19. The tests are labeled such that a clinician should consider the results of these assays as presumptive for risk of fetal infection with Parvovirus. The test may be used as an aid in the diagnosis of fifth disease or erythema infectiosum.

Regarding the public health burden, most individuals are infected in childhood, resulting in 50 to 80 percent IgG seroprevalence reported in serosurveys. However, much of the public health burden largely rests with a few specific populations. Chronic or reactivated infection can be associated with increased morbidity for high-risk populations, such as immunocompromised patients or those with hemolytic anemia. The virus can also spread through blood, and, therefore,

a pregnant person is at risk of passing the virus to the fetus causing serious complications due to severe anemia, such as hydrops fetalis, and miscarriage or intrauterine fetal death.

Risks to health are associated with failure of the diagnostic device to perform as intended or errors in the use of the diagnostic device or other reasons for false results and subsequently improper patient management. A false non-reactive result may cause spreading of the virus to other individuals through contact, and thus present a public health risk. Parvovirus B19 infection is generally self-limiting and benign for most healthy individuals, but, again, may pose a more grave threat of chronic or reactivated infection with associated morbidity for high-risk populations such as immunocompromised patients or those with hemolytic anemia, as discussed. The virus can also spread through blood. So, again, therefore, a pregnant person with Parvovirus infection with a false negative result is at risk of passing the virus to the fetus without the knowledge of the patient or the health care provider. This can cause serious complications such as hydrops fetalis, and miscarriage or intrauterine fetal death.

Even though there may not be a change in indicated medication administered in most circumstances, per se, FDA considers knowledge of the result and subsequent appropriate follow-up with ultrasounds, for example, to be a risk associated with these devices. A false reactive result may lead to the tested individual to be isolated and monitored for a short period of time, which could cause psychological stress, psychological stress specifically, particularly in pregnant people for the reasons that we discussed.

If Parvovirus antibody assays are reclassified as Class II, special controls would be written to mitigate the risks discussed on the previous slides. The goal would be to maintain consistent high performance across devices with similar intended uses and for individual devices over the total product's life cycle. There are some specific considerations for Parvovirus antibody devices and their validation. Specifically, there are very few Parvovirus antibody tests currently on the

market, which may lead to difficulty formulating a composite comparator during the clinical validation of a new Parvovirus test. Prevalence of Parvovirus IgM, even in the intended use population, can lead to difficulty in enrollment of IgM positive individuals in clinical and analytical studies. Confidence intervals around performance point estimates can, therefore, be quite wide; and, therefore, there can be some uncertainty about the performance of the tests, even in otherwise well-designed and/or enriched studies.

There are, of course, additional concerns related to cross-reactivity and interfering substances, along with other similar considerations for any other antibody tests. Regarding the additional considerations for the potential reclassification itself, manufacturers would no longer be regulated under the Class III paradigm, but instead under the Class II paradigm, which has fewer regulatory requirements. Manufacturers will no longer have to submit a PMA application for these types of devices but can instead submit a 510(k) to the agency for review prior to marketing their device. A 510(k) typically results in a shorter pre-market review timeline compared to a PMA application, which ultimately provides more timely access of these types of devices to patients.

Considering the probable health benefits of the use of these devices and the nature and known incidents of the risks of the devices, FDA on its own initiative is contemplating reclassifying these post amendments Class III devices into Class II. FDA believes that when used as indicated, Parvovirus antibody tests can provide significant benefits to clinicians and patients, including making a serological determination of past, recent, or current infection with Parvovirus B19 as an aid in the diagnosis of fifth disease or erythema infectiosum, and presumptive risk of fetal infection with Parvovirus B19. FDA's reasons for reclassification are based on the scientific and medical information available regarding the nature, complexity, and risks associated with Parvovirus antibody assays. The safety and effectiveness of this device type has become established since the initial approval of the first Parvovirus antibody assays in 1997.

We, therefore, have the following questions and requests of the panel. One, please comment on whether you believe FDA has identified a complete and accurate list of the risks to health presented by Parvovirus antibody assays. Please comment on whether you disagree with any of these identified risks or whether you believe any other risks should be included in the overall risk assessment of Parvovirus antibody assays. Please discuss potential mitigation measures/controls that FDA should consider that could mitigate each of the identified risks. And three, based on the information presented and future discussion at this panel meeting, please discuss whether, based on the available information, the panel believes FDA should initiate the reclassification process for these devices from Class III to Class II, subject to special controls. Thank you for your time.

Panel Questions and Deliberation

Dr. Van Der Pol: Thank you. The FDA has received no requests to speak during this open public hearing portion of the meeting. Therefore, we'll go to the next item on the agenda at this point. We will begin deliberations. But does anyone have a question for clarifying purposes of the FDA about the presentation we just watched? Seeing none, I'll move on.

Question One

Dr. Van Der Pol: At this time, let us focus our discussion on the FDA questions, which we just saw. You have copies of these questions in the packet of materials that you received in advance. I would remind each of you, when you begin speaking, to identify yourself so that we can facilitate transcription. If you would show the first question, please. This is going to be the same structure as what we went through with HBV where we're going to first focus on risks and whether the risks that were described are inclusive and exhaustive.

So do we have everything that we would like to see discussed as a potential risk? Are there any risks that were described that you think are not appropriate for Parvovirus antibody testing?

With that, if you want to raise your hand, we'll take comments. I know it's after lunch, but still we must all have some thoughts.

Dr. Moore.

Dr. Moore: Yeah. I guess I'm sort of curious what the impetus or what the reason is for having this come up for a discussion. Is there a paucity of tests for Parvovirus B19? I see two manufacturers on the accompanying sheet. I'm not quite sure what the rationale is for downregulating it.

Dr. Van Der Pol: I'll let Dr. Stenzel respond to that, but I'll also remind you that part of the FDA's charge is to have all tests classified at the lowest classification appropriate. And so at this point, do we have enough data to move it from a Class III to a Class II with appropriate controls? But Dr. Stenzel, in case I didn't cover that well.

Dr. Stenzel: Thank you, Dr. Van Der Pol. Exactly. We underwent a review of all Class III devices in microbiology, and we looked at those that we felt should be considered for down-classification. Typically, but not always, Class III devices do limit the number of options that are available to laboratorians, clinicians, patients, and it is our charge to make sure that tests are appropriately classified. We've previously underwent extensive reviews, and we're able to down-classify many Class II devices to Class I. So this is just an ongoing process to make sure that, when appropriate, we look at the possibility of down-classification. Some of my FDA colleagues may have something more specific to add about this particular analyte.

Dr. Van Der Pol: And I think the panel's charge is really just to say the FDA has gone through this data and put together data about it, but they want to verify that we don't identify any risks that they missed, and we're mitigating opportunities that they missed. So with that,

Dr. Pereira.

Dr. Pereira: Yeah. Marcus Pereira here from Columbia University. I imagine we might have some similar discussions with Parvovirus as related to also our prior discussion on hepatitis B. And I think some of it will relate around what exactly are the data surrounding the performance of these tests. In my practice, I don't often use it, being an adult transplant ID physician. Sometimes we use a pre-transplant, but I do get a sense that there is a significant rate of false positive results, particularly when it comes to the IgG, and some false negative results with the IgM. But in order for me to at least have a better understanding, would anyone here on this panel provide some data on the performance of these serological tests?

Dr. Karsner: Great. So I could probably shed a little bit of light on some of the data that we have at the FDA. So the performance of the test currently on the market, at least in the clinical validation that we reviewed at the time, the test did seem pretty specific or at least the negative percent agreement with immunofluorescence or Western blot or just a comparator, ELISA, that was already on the market, tended to be over 96%. For some of the tests, the sensitivity of the IgM specifically for acute infection in certain populations maybe it was a little bit lower than that, around 91 percent for those people, but it also depends on what is the comparator and how are you establishing clinical truth. But, generally, in the general population of the validation for the tests that are on the markets, the positive percent agreement with the comparator was between 97 and 99%. And then I can also speak to the fact that we checked our databases that we have to track errors that are reported to the FDA, and there were not a significant number of these tests having reported false results to the FDA, for what that's worth.

Dr. Pereira: Thank you. I mean, I think my particular concern would be when it's used for screening during pregnancy. Obviously, the stakes seem pretty high in that particular setting. And if you're telling me that the IgM has potential lower performance during that particular group, it

does raise some concerns and whether we could potentially have some special controls in order for that sort of high stakes situation, but I think we might have to discuss this a little bit more.

Dr. Van Der Pol: Sorry. I am muted. Dr. Blumberg.

Dr. Blumberg: Thank you. Emily Blumberg, University of Pennsylvania. Following on that, I do wonder how much of an access issue there is with this particular testing. As opposed to hepatitis B, where I think we would have to say this is a global concern and an enormous number of people affected, many of whom are in resource limited areas where access to testing really is a concern, do we have any data to share in terms of that? I assume in terms of validation of the testing, regardless, there would still need to be some way to validate any test, regardless of where it's at in terms of that.

Dr. Van Der Pol: Dr. Stenzel.

Dr. Stenzel: Yeah. I'm not sure. The FDA doesn't always have information about access to testing. More options are better, if they're good options. Again, the consideration of moving from Class III to Class II is are there special controls that can mitigate risk? And, as Dr. Van Der Pol raised, we're looking, whenever possible, to down-classify. This does intend to provide more options for tests that laboratorians and clinicians and patients can choose from, and it's our belief that that's a good thing, as long as we can mitigate the risk.

Dr. Van Der Pol: Dr. Procop.

Dr. Procop: Yeah. I share some of the same concerns that Dr. Pereira raised, and I think it all depends on use case. Unlike hepatitis and HIV, it hasn't been my experience that individuals with positive antibody tests automatically get a PCR. It's kind of does it fit clinically, or doesn't it? So I really don't have a great concern about some misses of fifth disease. But, like you said, during pregnancy, aplastic anemia of immunocompromised hosts, I think that's where the special controls might be particularly applicable to how you're using the test. And in those situations, you may

want to follow up with a more definitive nucleic acid test in a positive that could be a false positive. I'll stop there.

Dr. Van Der Pol: Thank you. Dr. La Hoz.

Dr. La Hoz: Yeah. I think there are multiple considerations. My understanding is that in pregnancy, what we are going to be focusing on, is the risk for hydrops fatalis, which if the pregnant female already has a positive IgG, it means that there's no risk. So at least from the numbers that we've been quoted for the performance of the IgG, it appears that it may perform well in that scenario. I think pregnant females are going to be in different areas of the country where potentially more options for testing could be helpful. On the other hand, in the immunocompromised host, we do see pure red cell aplasia from Parvovirus B19, and the IgM is a unreliable test to diagnose the infection in immunocompromised host, and it often requires a PCR to compliment the diagnosis, as well as, you know, chronic arthritis in that population may also benefit from a PCR, and already the IgM and at least one of the testers here in the materials that we have may have a PPA of 78%. Maybe my only question for the FDA is what is the track record over all of these assays? Similar comments to what we made to hepatitis B. I mean, this test appears that one was approved in '99 and the other one in 2017. So, there may be some information.

Dr. Van Der Pol: Dr. Petti.

Dr. Petti: Dr. Petti, Health Spring Global, following on what Dr. Procop and Dr. La Hoz said, special controls, I think, are very important if we reclassified a Class II. I do use Parvovirus serology testing in the non-immunocompromised hosts and often do the acute and convalescent pair sera. So perhaps in product labeling giving some guidance that, again, "used in the aid of the diagnosis of" could be very valuable, particularly for those institutions where it could take a week to 10 days to get a Parvovirus viral load back, the clinicians who don't have access to viral loads in a rapid fashion.

Dr. Van Der Pol: Thank you. Dr. Caliendo.

Dr. Caliendo: Angie Caliendo, Brown. So I think the FDA has outlined appropriate risks. I don't have anything to add to that. But I do find it very interesting that almost everybody has mentioned PCR for Parvovirus, and there's not even a test available. So maybe one of the mitigating measures needs to be the FDA finding a way to maybe use a de novo 510(k) to help companies get a quantitative cargo PCR out there, because that's the test many people are using clinically. So that's that. I don't have anything to add to the risks. I think they're covered, but when we get to mitigation methods or mitigation suggestions, that would help, I think, put a clinical context on a result.

Dr. Van Der Pol: Thank you. Dr. Karsner.

Dr. Karsner: Yes. I just wanted to address the question of the track record for these tests. So the information that we have is the performance and the validation that was included in your packets, as well as the kind of post-market evaluation, or at least reporting systems that the FDA has where we have not really received reports of false results for these assays. So that's the information that we have about the track record for these tests.

Dr. Van Der Pol: Dr. Stenzel.

Dr. Stenzel: Yes. And I wanted to respond in particular to Dr. Caliendo's comments that there is no approved PCR test. And part of what we're doing here is looking at is this ready to be down-classified in general. We hope that invites, if it can be mitigated and it can be safe as a Class II device, we believe it would encourage developers to take a look at this. I do have to state that even if we down-classify, and we have all of the measures in place to make sure it's safe and they're appropriate, the FDA does not develop tests. And we can't compel people to come in with their submissions. What we can do is make sure that the classifications are as low and appropriate as possible so that it's as easy as possible, should we say, for developers to come in. Thank you.

Dr. Van Der Pol: Angie, did you want to say something?

Dr. Caliendo: Angie Caliendo, Brown. So, Tim, thank you. Because I think that's where the real value here is, right, if we can down classify and that gives you the ability to make it easier for a PCR assay to come through? You're right. We all know we can't beg, borrow, and steal sometimes to get manufacturers to make tests, but that is probably the real value here. So thank you for that clarification.

Dr. Van Der Pol: And I have a clarifying question for Dr. Stenzel as well. And that is, this topic was focused on Parvovirus antibody tests. Is it a potential for the panel, based on some of our discussions when we get to question three about do we recommend down-classification, could we recommend that that down-classification is more broad than just antibody tests but any Parvovirus test? Because I think that's one of the things maybe I'm hearing as I'm making notes.

Dr. Stanzel: Yes. Tim Stanzel. That would be very helpful. It would be difficult for us to receive a DNA based test and say it's okay to be Class II while we have these other tests that are Class III. That would be confusing to developers in the community. So that would be extremely helpful.

Dr. Van Der Pol: Excellent. I think that gives us some guidance. I'm going to just go back and see if I can wrap up question one, which was about risks. I heard a couple of people say that they think all of the risks have been included and are appropriate. I want to give everybody one last chance in case there are any risks that they would like to speak of that we haven't mentioned that aren't included in the FDA's considerations.

Dr. Chiu.

Dr. Chiu: I'm sorry. I was on mute. Sorry about that. Yeah. I just wanted to comment that I feel that the FDA has adequately described the risks associated with this particular test, but the only comment that I had was that I feel that the special controls have to emphasize kind of the intended use. Because I would say like an identified risk would be that the test is ordered inappropriately. And in addition to that, the test is interpreted, or the results are maybe incorrect.

There would be a risk of kind of inappropriate use of the test. And so identifying, providing specifics regarding the intended use population and regarding the clinical use cases, as others have alluded to, I think would be really important.

Dr. Van Der Pol: Any other comments about risk? Okay. Seeing none, I'm going to summarize.

I think that the panel in general feels like the risks described by the FDA are appropriate, and that they've captured all of those risks. The concerns that were raised by the panel were whether or not those risks would perhaps also need to include special controls for special populations and getting back to intended use. So I think this is true, especially for use in pregnant women. I think that also probably there need to be risks that maybe are associated with ordering appropriately, especially as it relates to IgG versus IgM because those have very different interpretive values, and potentially that the risks of false negative and false positives apply as well to other Parvovirus types of testing, which would include molecular tests for DNA.

So, Dr. Stenzel, does that give you the information that you need for question one?

Dr. Stenzel: It does. And no follow-up questions. Thank you.

Question Two

Dr. Van Der Pol: Perfect. Okay. So then let's move on to question two, which we've already talked about a little bit, which is what are the mitigations and special controls that the FDA should consider in order to address those identified risks?

We've already talked about making sure that there's appropriate labeling to clarify intended use, clarify when it's appropriate to order the different tests in different populations, and how to interpret the tests. Are there other mitigations that we need to consider as well for Parvovirus testing? And remember that we can be a little bit more broad and include mitigations or special controls that we think would be appropriate, excuse me, for DNA based PCR type testing, as well

as for antibody testing. So if anybody has any other special controls, other than labeling and intended use statements and making sure that sensitivity and specificity are set at appropriate levels.

Dr. La Hoz.

Dr. La Hoz: This is Ricardo La Hoz from UTS. I don't know if this applies to the question, but transplant recipients often receive IVIG as treatment for rejection or donor specific antibodies, and it is always challenging to interpret serological assays in patients that have received this type of products. And then, as I mentioned before, the performance of a serological assay in an immunocompromised host. But I'm unsure that that really answers the question that you were on with that comment.

Dr. Van Der Pol: I think it does because I think you're saying that here's a population that needs special intended use comments or labeling comments about how to interpret those results, and this may be the point at which you say that one of those mitigations is reflexing to a molecular test, right, as opposed to just making a treatment decision based on an antibody test alone? Other mitigations? Dr. Ng?

Dr. Ng: Well, of course, you opened that door, Bobby. In situations of immune perturbations, and that includes pregnancy, what is known about reactivation of latent disease? And then if we're going to bring in viral loads, what's the relationship of a viral load to infection and transmission versus just reactivation without clinical consequence?

Dr. Van Der Pol: So the relationship of viral load to clinical outcomes?

Dr. Ng: What's the clinical usefulness of a viral load? Is there a threshold that tracks with infection and transmission?

Dr. Van Der Pol: I'm going to pass this off to Dr. Caliendo, who is more knowledgeable than I am.

Dr. Caliendo: No. I can't answer that question, and I don't know that anybody can. And I think that's one of the questions that needs to be addressed, which is why a molecular assay to be clinically useful needs to be quantitative?

Dr. Van Der Pol: Yeah. I'm not sure that it does.

Dr. Caliendo: Because there is this low-level reactivation. I haven't seen data, value on exactly what that threshold is, and it's probably different in different patient populations, but that's a clinical question that needs to be addressed. And that would be, I think, the test, as opposed to a qualitative assay. That might help. I mean, it depends if you're testing amniotic fluid versus blood, right, and what the patient population is? But I think it's very interesting, which makes my special controls is I think molecular is you would have the same performance characteristics that you would of any viral load assay. And it may be one of those that we need to test so that we can actually address some of these important clinical questions. It is interesting that you could put as a special control to reflex to a molecular test when there isn't one available that's gone through the FDA process. So is that okay to do?

Dr. Van Der Pol: I mean, I think that we're just throwing out ideas and possibilities. Just because we've said that in this panel discussion doesn't mean that will be one of the special controls.

Dr. Caliendo: How is that even possible that we would say something, and they wouldn't absolutely do it?

Dr. Van Der Pol: I don't know. For years I've not known that.

Yeah. Dr. Karsner, would you like to provide clarity where I have provided muddiness?

Dr. Karsner: Sure. I'll just address two things. One is that, generally, for a lot of our serology tests that we regulate, labeling includes limitations about caution in interpreting serology test results in immunocompromised individuals for the reasons that we've discussed. And just to sum

it up, I think it has to do with the etiology of immunocompromised can be very different depending on who the person is, what's going on, what medications they're taking, et cetera. And then the degree of immunocompromised, we don't always know how to interpret serology results in general in those populations. And then the other question about trying to interpret a viral load in respiratory diseases is quite challenging. I think we borrow the idea of viral load from diseases like HIV and CMV, well, an HPV, for example, where we have kind of established, for some of them, medical decision points at certain concentrations in blood. But I think we saw with COVID, trying to interpret a pathogen burning in a respiratory specimen as it relates to infectiousness is really challenging also, because infectiousness has to do with the amount of time someone is exposed and how good is the ventilation in a room, and all those sorts of things. So I think there are a lot of challenges with that.

Dr. Van Der Pol: Dr. Caliendo.

Dr. Caliendo: Angie Caliendo, Brown. Let me just clarify. I wasn't talking about the respiratory compartment. I was talking about blood.

Dr. Karsner: Oh, okay.

Dr. Caliendo: Just because I agree totally with what you say with respiratory, but just to clarify.

Dr. Karsner: Okay.

Dr. Van Der Pol: And I think the larger concern is about vertical transmission, right? I mean, that's what we're kind of focusing on thinking.

Dr. Karsner: I see. Okay.

Dr. Van Der Pol: Oh, any other mitigations other than labeling and, you know, indications about appropriate use, again, keeping sensitivity and specificity at higher levels, which I think the FDA has data for already. Okay.

Seeing no more conversation on this, I will summarize that I think, in general, the panel agrees that special controls, we understand probably what those need to be, and they need to be population specific. And they need to include labeling, and they need to include appropriate sensitivity and specificity performance measures, especially understanding specificity of IgM, as well as sensitivity of IgM, because that's going to perhaps be used more often during pregnancy. But all immunocompromised patients need to have appropriate safety measures, warning labels, and limitations to interpreting these results. I think that pretty much covers it, and I think that the panel didn't have specific concerns about what those labels or limitations should look like.

Dr. Stenzel, did you need more information from the panel.

Dr. Stenzel: I think that's very helpful and thank the panel and no follow-up questions. Sometimes biology limits sometimes what you can do. And that doesn't mean you don't test. It just means you need to understand the limits of that test and make the appropriate laboratory and clinical decisions. Thank you.

Question Three

Dr. Van Der Pol: Okay. So, this moves us on to question three, which is always the fun question. So if we could get the panel to summarize basically if they believe there's enough information to allow reclassification of these devices from Class III to Class II, subject to special controls and other mitigating processes.

So with that, we can kind of go around the room, if you'd like, I'll just call on people, or if you'd like to raise your hand. There we go. Cathy.

Dr. Petti: Cathy Petti, Health Spring Global. I think we should, again, just go back to refocusing our conversation on the technology and the experiences and data that we've had thus far with serology testing. We all have used it a lot in clinical practice. We all understand that a single point in time test may not be indicative of a diagnosis, and that repeat testing, either acute

or convalescent or reflexive to a molecular test, is commonly used in practice. So I think with the data available to us now, I believe reclassification to Class II is safe and would be effective.

Dr. Van Der Pol: Dr. Caliendo.

Dr. Caliendo: And I agree. Oh, Angie Caliendo, Brown. I agree.

Dr. Van Der Pol: Dr. La Hoz.

Dr. La Hoz: Ricardo La Hoz from UT Southwestern. I agree.

Dr. Van Der Pol: Dr. Beavis.

Dr. Beavis: I agree as well. Kathleen Beavis, University of Chicago.

Dr. Van Der Pol: Dr. Pereira.

Dr. Pereira: Marcus Pereira, Columbia University. I agree as well. I actually think reclassifying as Class II would be a great progress. It sounds like we don't have enough tests for Parvovirus, and actually lowering the threshold would potentially lead to more tests becoming available.

Dr. Van Der Pol: Mr. Spring.

Mr. Spring: Yes. Thank you. Brad Spring with Roche Diagnostics, and I agree with Dr. Pereira's comments there, too. I agree with down-classification. I think it would open up the market for more of these tests to come into play.

Dr. Van Der Pol: Dr. Chiu.

Dr. Chiu: Yes. Charles Chiu, UC San Francisco. I agree with down-classification.

Dr. Van Der Pol: Thank you. Dr. Blumberg.

Dr. Blumberg: Emily Blumberg, University of Pennsylvania. I agree with down-classification.

Dr. Van Der Pol: Dr. Wentzensen.

Dr. Wentzensen: Nicholas Wentzensen from NCI. I agree with down-classification.

Dr. Van Der Pol: Dr. Walker?

Dr. Walker: Dr. Roblena Walker. I also agree.

Dr. Van Der Pol: Dr. Moore.

Dr. Moore: I think Dr. Petti summarized it beautifully, and I have nothing to add. I agree.

Dr. Van Der Pol: Dr. Kotton.

Dr. Kotton: I also agree with down grading.

Dr. Van Der Pol: Dr. Ng.

Dr. Ng: Can't we just do a thumbs up?

Dr. Van Der Pol: Sure! Everybody want to do a thumbs-up?

Dr. Ng: That would be a lot faster, right? This is not controversial.

Dr. Van Der Pol: Thank you. I don't know why you didn't tell me this five minutes ago. All right. You want to thumbs-up me?

Mr. Spring: Well, does that work with the recording?

Dr. Van Der Pol: Oh, well, since we're not voting, I think it's fine because I can say that we have a true consensus here. We don't have any concerns to share with the agency. Everybody is generally supportive of the fact that there are sufficient data to help develop special controls and labeling, et cetera. So, we would strongly recommend that the agency consider down-classifying the Parvovirus antibody tests.

Dr. Stenzel, do you need any more information from the panel about this topic?

Dr. Stanzel: Well, I just want to make sure that if somebody wanted to say something and not just put thumbs up, that they're welcome to do that. This is the time for the FDA to get input, and we really do value that input. And with that, we have what we need, but if someone wants to say anything else, I see there's a few hands still up. So we welcome that input as well. But I defer to you, Dr. Van Der Pol.

Dr. Van Der Pol: Let's see, Dr. Kotton.

Dr. Kotton: Oh, sorry. My hand was up. It was a stray. Sorry.

Dr. Van Der Pol: I usually leave myself on mute and leave my hand up and my thumb up. So I'm right there with you. Does anybody want to add anything to this conversation? I think this one was a fairly easy one for us to think about. So that's probably why the conversation was a little bit less intense.

Okay. At this time, then, we are ready to begin our third and final session of the day. I'd like to invite the FDA to start their final presentation. Again, I'm going to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel chair.

FDA Presentation

Dr. Van Der Pol: FDA, you may now begin your presentation.

Dr. Gerald: My name is Noel Gerald. I'm with the Division of Microbiology Devices in OHT 7 OPEC. And I'm going to talk to you about potential M. tuberculosis interferon gamma release assays device reclassification. The purpose of this meeting is to discuss the potential future reclassification of mycobacterium tuberculosis, which I'll refer to as TB, cell mediated immune reactivity in vitro diagnostic devices such as interferon gamma release assays, which I'll refer to as IGRAS. FDA is seeking recommendations from the panel members and the public on whether sufficient information exists such that the development of special controls, which along with general controls, can mitigate the risks from these devices, such that the devices would provide a reasonable assurance of safety and effectiveness and, therefore, can be eligible for a Class II designation.

I'm going to talk a little bit about the public health burden of TB. You can find these details and a lot of additional details about this in the executive summary. TB case counts and incident rates have steadily decreased in the US over the past 30 years. 8,300 reported TB cases were in

2022, which is two and a half cases per 100,000 persons. Case counts are returning to pre-pandemic levels following declines in reporting during the previous two years. CDC estimates that up to 13 million people in the US could have latent TB. Worldwide TB burden is estimated at 10.6 million persons, and globally 1.6 million people died from TB in 2021.

As a few additional details, pulmonary tuberculosis is the most common clinical presentation of tuberculosis in adults, and infection occurs by transmission of the organism through inhaling airborne particles that contain MTB that are released from individuals with active pulmonary disease. Most people who are infected with TB are asymptomatic, which is known as latent TB infection, and the latent infections are not contagious and do not result in clinical disease in most cases. But, overall, there's a five to ten percent lifetime risk for patients with latent infection to develop active TB disease. And this risk varies to many factors, including immunosuppression. Of the United States TB cases, more than 80 percent are attributed to reactivation of untreated latent TB. There are numerous antibiotic regimens available to treat TB. However, adverse drug reactions are common, and patients should be closely monitored while on therapy.

A little bit more about interferon gamma release assays, IGRAs. IGRAs are indirect tests for TB. They're in vitro blood tests which measure T-cell release of interferon gamma following stimulation with TB antigens to aid in the diagnosis of TB. The commonly used ESAT-6 and CFP-10 IGRA peptide antigens are specific to organisms in the Mycobacterium tuberculosis complex, but they're absent from the BCG strains that are used in vaccines and most non-tuberculous mycobacteria. The IGRAs are useful in BCG vaccinated persons and in clinical scenarios where a single patient visit is advantageous. In contrast the tuberculin skin test, TST, is another type of indirect test for TB which requires a second patient visit 48 to 72 hours after administration. Additionally, it is known that prior BCG vaccination or infection with non-tuberculosis mycobacteria can cause a reaction in the TST.

So this is a slide with a mock intended use statement of a TB IGRA. I'll just walk through it briefly. Here we've mentioned the assay name is an in vitro diagnostic test using a cocktail of TB antigens, which would be described to stimulate cells in whole blood, typically, the detection of interferon gamma by, we would describe the specific technology used, is used to identify in vitro responses to these antigens that are associated with mycobacterium tuberculosis infection. The assay is an indirect test for M. tuberculosis infection and is intended for use in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations.

So here is a list of the PMA approved TB aggregates. These are all qualitative tests. The first one was approved 22 years ago in 2001, and the technologies have continued to evolve for things like sample processing and test interpretation. This slide also includes some of the performance estimates that can be found in the approved labeling for each of these tests. As there is no true reference standard for TB infection that's applicable to all cases, sensitivity here is estimated as compared to culture in a population with confirmed pulmonary TB disease. And then specificity is estimated in a population of subjects with low risk of TB infection. There are other populations that are included among the clinical evaluations to validate these tests. And I'll talk about some of those a little bit later in this talk.

But these are the risks to health of inaccurate results that we've identified: False negative results, incorrectly operating a device causing false negative results, and incorrectly interpreting results as negative. Results can lead to progression of active or reactivation of latent TB disease in individuals, spread of disease in the community, or missed opportunities for diagnosing an underlying condition or disease such as HIV infection that may have been unrecognized and may be contributing to the progression to active TB. False positive results, incorrectly operating the device causing false positive results, and incorrectly interpreting results as positive results can lead to unnecessary treatment within the associated drug toxicities for these therapies, unnecessary

patient isolation and radiologic imaging and laboratory testing, and unneeded contact tracing, resulting in wasted healthcare resources.

So aspects of IGRA device validation, labeling, and use that should be taken into consideration when thinking of potential mitigations are discussed here. You know, so labeling includes clinical performance in several different populations, you know, which include, as I mentioned, patients at low risk for previous TB infection in the absence of risk factors, patients with culture confirmed or NAT confirmed active pulmonary TB infection, patients at high risk of latent TB, and patients with a history of non-tuberculous mycobacterial infection or colonization, which could be cross-reactive. So the labeling includes the performance estimates, as I mentioned. These are truly estimates in the absence of a reference standard. The specificity is estimated in comparison to the expected negative results for a population at low risk of TB infection. And sensitivity is estimated from the population with active pulmonary TB. Labeling can also include performance as additional information agreement to other indirect tests. So positive percent agreement or negative percent agreement for the results of the TST test or another IGRA.

The labeling does highlight the limitations of studies conducted in the absence of a true reference standard, and it includes other limitations that are relevant, such as a negative result does not exclude the possibility of infection within tuberculosis and noting that these tests should not be used alone. They must be used in conjunction with each individual's epidemiological history, current medical status, and the results of other diagnostic evaluations. So other things to take into consideration include the years of experience the clinicians have had at this point on recognizing the limitations of these tests and considering the appropriate uses. And then also the existence of guidelines from organizations such as the American Thoracic Society, CDC, and IDSA that explicitly discuss the appropriate use and interpretation of these tests.

So, lastly, some additional considerations for reclassification. Reclassification has the potential to increase opportunities for innovative diagnostic devices in this space. There would be reduced regulatory requirements for sponsors and manufacturers. So PMA specific requirements would be removed, but the belief is that the risks can be mitigated by special controls.

So these are the questions for the panel. One, please comment on whether you believe FDA has identified a complete and accurate list of the risks to health presented by M. tuberculosis assays, in this case, specifically, interferon gamma release assays. Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment of M. tuberculosis assays. Please discuss potential mitigation measures or controls that FDA should consider that could mitigate each of the identified risks. Based upon the information presented and future discussion at panel meeting, please discuss whether, based on the available information, the panel believes FDA should initiate the reclassification process for this device from Class III to Class II, subject to special controls. Thank you.

Dr. Moore: Are you on mute, Bobbie?

Dr. Van Der Pol: It is always the best way to deal with me. We are scheduled for a 15-minute break now, and I think we'll go ahead and take that in case people need to stand up and refresh, and then we'll have our discussion about these questions when we come back. So, if you could be back on camera in 15 minutes, that would be wonderful. Thank you.

Q&A with FDA

Dr. Van Der Pol: Thank you. I'd like to resume the panel meeting. At this point in the agenda, we have space for open public hearing. But the FDA received no request to speak during this

portion of the meeting, so we'll continue with the agenda. Before we begin deliberations about the TB IGRA assay, does anybody have brief clarifying questions for the FDA?

Mr. Spring.

Mr. Spring: Yeah. Brad Spring with Roche Diagnostics. I am not sure if everybody knows, you've previously down classified other tuberculosis assays, correct, to Class II?

Dr. Gerald: Yeah. This is Noel Gerald, Assistant Director of Bacterial, Respiratory, and Medical Countermeasures. Yes. We did reclassify molecular tests on NAT assays from Class III to Class II.

Dr. Spring: Thank you,

Dr. Van Der Pol: Dr. Ng.

Dr. Ng: I'm sorry. I just would like clarity. As I understand, these IGRAs are primarily used to identify latent TB, but the positive predictive agreement is based on active TB, correct?

Dr. Gerald: Yeah. So actually the intended use doesn't explicitly state latent TB. We understand that that's a big part of how they're used clinically. And it's just part of that also is it's very difficult to conclusively show that someone has latent TB until it's progressed to active TB. So it's part of the issue when we say we can't adjudicate every single case of TB, and why we don't have a true reference standard. And so, it's why we've had to take this approach of having these kind of well-defined benchmarks that we can kind of assess performance, and then evaluating the performance in other populations.

Dr. Van Der Pol: Dr. Chiu.

Dr. Chiu: Yeah. I had one question for the FDA. So, one thing that was mentioned in the presentation is that potentially by down-classifying this category of assay, it might potentially open the way for other kind of tests in that category. My question is specifically, are you referring to a category of, it's a very broad category, of potentially human host response biomarkers, or are you referring to it because that's the, that is what makes this test, I think, a little different than other

tests that look directly for either nucleic acid or protein from the pathogen, but rather focus more on the host response. And so I'm wondering is that what you're referring to that it might open up assays in the future based on host response for infectious diseases?

Dr. Gerald: Yeah, I'll take that. Noel Gerald, FDA. No. I don't think that we were specifically indicating or meaning to imply biomarkers in general, right? So it is really specifically on cell mediated immune response assays, the same way we have humoral like antibody response. So that was the intent.

Dr. Van Der Pol: Dr. Kotton.

Dr. Kotton: Camille Kotton, Mass General. I would just like to emphasize that this field will probably be growing. So we've had CMI tests for tuberculosis for a long time now. I think it's definitely time to consider downgrading them. There are some nonspecific immunologic markers that are summated immunity based and then some specific CMV type tests. So I think the field is growing, and I think we should be sort of thoughtful about that, or at least I would encourage the FDA to be thoughtful about that, as that field is likely to grow. My second comment relates to the fact that these are lymphocyte-based assays, and I think many of us on this call who deal with immunocompromised patients experience a lot of issues with a lymphocyte-based assay, especially when they are used in patients on very potent immunosuppression and whatnot. It doesn't mean that they shouldn't be downgraded per se, but I do think that clinical context is important. We often see them being used to do things like rule out tuberculosis and other things that infectious disease specialists kind of come upon where we need to do some educating. So it's sort of a new field. There are a bunch of caveats. That being said, I think it would be reasonable to consider downgrading. Yeah, it's a new field.

Dr. Van Der Pol: Okay. We're still in the phase where the only thing I'm asking from you right this second is if you have clarifying questions for the FDA. So if that is a true statement, then Dr. La Hoz.

Dr. La Hoz: Yeah. I think I just had some big picture comments and then answers.

Dr. Van Der Pol: If you have comments, let's hold those till we get into the comments section, but I'm just trying to make sure that everybody has a chance to ask the FDA what they are asking of us. So if you have any clarifying questions, feel free. Dr. Pereira.

Dr. Pereira: Yeah. I think the data was provided in terms of positive predictive and negative predictive. Were there any data on this particular for the quantifier on test in terms of indeterminate results, how often those come back? And I think that sort of alludes to all the transplant providers over here that we often see that result. And we'll be talking about that in terms of sort of identifying some risks that perhaps special controls could be developed around. But any data around sort of how often those results come back?

Dr. Van Der Pol: Dr. Gerald?

Dr. Gerald: Yeah. So I think that for FDA, really the main information that we have is in the labeling, so the rate of indeterminate results that are observed there. I think what you're getting more to the question is the follow-up, right? So these labels are usually pretty explicit of what should be your next step to what you should be thinking of next when you get an indeterminate. So I don't think that we have a good idea in practice of then what happens to that indeterminate the next time someone does a test. So I think that's probably what you're asking. But I think mainly what we know about the rate of indeterminants is that first time and what's seen in those validation studies.

Dr. Van Der Pol: And I would point out to people that while, in the data that the FDA presented, one of these assays has been, was approved more than 20 years ago, it's actually the

same assay with a different kind of parent company now that got approval in 2019. It's still the QuantiFERON assay. And so, I mean, I think that it's worth noting that we really basically only have two assays on the market for this purpose. And whether or not that makes any difference, I don't know. Just something for you to think about.

FDA Questions

Dr. Van Der Pol: So with that, let's focus our attention on the questions that they've asked of us. You have copies of the questions in your packages. I would ask that each of you identify yourself each time that you speak.

Question One

Dr. Van Der Pol: So with that, question number one, which I think we all know by now is do you think that the risks are fully described, and do you think that there are any risks that are described that don't belong that need to be removed? And the risks were false negatives and false positives, either from operating the device incorrectly or just incorrectly interpreting the device, or just the device not performing as well as it might have. So do you think those risks are sufficient?

Dr. Blumberg.

Dr. Blumberg: Sorry. I was having trouble unmuting. Emily Blumberg, University of Pennsylvania. I think the risks as described are accurate. But the issue, and I think Ricardo was talking about this and Camille a little bit too, is that there's so much that's population-based risk, and so quantifying the risk really varies based on the population you're doing this in. So clearly the risk of an indeterminate or inaccurate response is greater in immunosuppressed populations. It's also greater in people with active infection. And so I think that it's just important that we add to what was stated that these risks may be greater in some of the populations where you're most

interested in the answers, the immunosuppressed, the person who comes in with symptoms, because the test is currently used or often inappropriately used to make a diagnosis of active TB.

Dr. Van Der Pol: Thank you, Dr. La Hoz.

Dr. La Hoz: Yeah. Emily made some of my comments. So I would say that for a disease that probably involves one out of four people living in this world, that's a latent TB, and probably the number one lead infectiously in cause of death, and now number two after COVID, it's surprising that we only have a few tests in the market to try and mitigate a disease that, if we identify it on the latent state, we have pretty good preventive measures, meaning latent tuberculosis therapy. So I do think that the risks have been identified correctly. I'm probably going to repeat what's been mentioned before, but number one is that person that may receive a biologic or may just be being screened for latent tuberculosis for XYZ reason but has a low pretest probability. So that's a population in which we need to be careful about false positives. Number two is the well-known fact that not everybody that has active TB is going to have a positive TB IGRA test result. That is a known fact. And then what's been alluded before is all those already immunocompromised hosts that have these tests that may have a false negative test. But I do think that the risks have been adequately identified of false positives, false negatives, and I do think that there's ways to probably mitigate this risk by labeling, establishing standards in different populations like it's been alluded to in the FDA presentation. And I think we need to try and make this more available because this is a disease that's quite preventable by correctly identifying those with latent TB.

Dr. Van Der Pol: Dr. Stenzel.

Dr. Stenzel: Yes, thanks. Thanks for all the comments so far. I did want to state that the limitations in the labeling of these tests does specifically mention care in immunocompromised population. I also wanted to state something that may not be obvious to everyone. So we have two providers in the United States of this important testing category. And even though they're approved,

it doesn't mean their work is done. So there is more annual work to do to maintain these approvals. And then if they want to make any changes, it's more difficult to make changes, for the benefit of patients and clinicians and laboratorians, with a PMA. And then also if they need to move or expand their manufacturing footprint, they need to submit that to the FDA, and then they need to be inspected. And having personally been responsible for three PMA moves in my career prior to joining the FDA, I can testify how difficult that is. So even though there may be a few, we also are concerned about the right classification to help them maintain their market presence and help ensure that they're continuing to be able to be available for use. Thank you.

Dr. Van Der Pol: Yeah. You would hate to see somebody drop their manufacturing because they couldn't deal with the regulatory environment. That's a true statement. Did other people have comments about the risks as described? Were there any? We have discussing specific populations, particularly immunocompromised people and populations with low positive predictive values.

Dr. Beavis.

Dr. Beavis: Thank you. Kathleen Beavis, University of Chicago. Yeah, especially having heard what Dr. Stenzel just said, there's a real risk if these leave the market. In our ancient memory, when people used to get skin tests, even in a captive hospital population, when I was at Cook County and we were very aware of TB testing, over a third of employees wouldn't return to get their skin test read. And that is a real risk if these tests do disappear from the market and can't continue to be improved.

Dr. Van Der Pol: Dr. La Hoz.

Dr. La Hoz: Yeah. I think Dr. Beavis makes a spectacular point because the difference between the PPD and this assay is that the PPD is very user dependent on who reads the assay. And I think there is a much higher risk of false positives because the area of induration with PPDs is

misinterpreted by the area of erythema. So, losing such a test, when one of the four people living in this planet could be, could have latent TB, could be a high risk.

Dr. Van Der Pol: Yeah. And right now we're focusing on risks of the tests that the test causes to patients. So does anybody have any additional risks that they'd like to add or any risks that were described that they think shouldn't be on the list?

Dr. Pereira.

Dr. Pereira: Yeah. Marcus Pereira, Columbia University. So, in addition to the indeterminate results and sort of all of its misinterpretations, which should be included here as a risk, the only other thing I can think of is sort of follow-up testing, sort of repeat quantifier on tests. So if you've had a positive test and you were treated, sort of the potential lack of necessity in repeating that test. And that certainly could lead to potential unnecessary retreatments. So that could be a potential risk here if it's sort of not used in accordance, in terms of what the test represents.

Dr. Van Der Pol: Dr. Petti.

Dr. Petti: Cathy Petti, Health Spring Global. One more risk is for those that are false positives and then a subsequent workup is required. We missed adding that then they are being delayed for treatment for their Crohn's disease or rheumatoid arthritis. So they're being delayed to treatment. That could be associated with significant morbidity.

Dr. Van Der Pol: Okay. Dr. Kotton.

Dr. Kotton: Two things: One, if we were to lose this testing and revert back to PPD testing, we would miss a huge number of cases of latent disease, especially in people on dialysis or with cirrhosis or any kind of major comorbidity. The PPD testing is a lot less sensitive. So that would really be, in my practice, pretty disastrous. I actually stopped doing skin testing about a decade ago because, as was nicely outlined, people actually just don't come back for follow-up testing, which is a big issue.

The second thing I wanted to highlight, and I'm not sure if it really belongs here. In a way, it sort of doesn't necessarily relate to downgrading, but I just want to highlight, and I'm not sure how the agency is aware of this, but so with QuantiFERON testing, you get either positive, negative, or indeterminate results. And with T-SPOT, it's either positive, negative, or borderline. And that indeterminate tag is really problematic. I think all of us on this call probably understand what it means. But when I give lectures on this subject, many people come up to me and say, don't you know that indeterminate means that they should get latent TB prophylaxis? And I give nine months of INH. And so there's a huge amount of confusion. I'm like, oh, no, it just means the test didn't work. And they're like, no, no, indeterminate means, and I'm like, no, it doesn't. I said, it's the same as though they dropped the test tube. So it's not valid data, right? And so I just wanted to highlight that as an issue. In a way it doesn't relate to downgrading, but for me that's one of the bigger issues with this testing, especially because a lot of testing gets sent like one day after liver transplant. So it's always indeterminate, and then people call me about that. So it would be helpful to have some guidance there, but that might be for a different day.

Dr. Van Der Pol: Dr. Gerald.

Dr. Gerald: Yeah. I definitely acknowledge what Dr. Kotton just said. It is something that we've run into also when talking about equivocal for other tests, this kind of vagueness of use of the terms indeterminate, equivocal, or borderline. And it is something that we have been trying to be a lot more explicit about when we're talking with the sponsors going forward. So your point is very well taken.

Dr. Van Der Pol: Any other comments about the risks of the actual incorrect results? I think then that I will summarize.

What we're hearing in general is that the risks were captured. We didn't have any risks that you showed that we thought should be removed from the list. However, the risks list could benefit

by calling out specific populations in which those risk levels were higher, as opposed to others in which maybe it was lower, obviously, immunocompromised people, but also those people with active disease for whom the risk of a false positive might be more relevant, but also the risks in populations at low risk or low prevalence of disease where the positive predictive value might be quite low. And so the risk of a false positive. So both false positives and negatives are already described on there, but the panel felt like maybe they should be described in more specific detail for different populations. And also one of the risks that didn't appear to be included was the risk of an indeterminate result, because that did have clinical ramifications, and people have had to deal with that in different ways. And then, finally, the risk of inappropriate use, which you specifically mentioned in the risks that are listed the risk of incorrect use, but, again, it's probably worth listing the risk of people ordering this test when this test is not appropriate for that particular patient. And one of the risks that specifically could be called out was when you have an incorrect result that could lead to treatment delays for other diseases. And so perhaps that was worth calling that risk out as well. Okay. And that was pretty much all of the list of comments that we had about the risk assessment as provided.

Dr. Stenzel, was that sufficient?

Dr. Stenzel: Yes. No follow-up. Thank you.

Question Two

Dr. Van Der Pol: Great. So let's go on now and discuss mitigation, which I think people, we're all in that boat where we kind of talk about both at the same time because they go together for us. But let's discuss the potential mitigation measures you'd like to see in place for assays that are classified in Class II and special controls the FDA should consider to mitigate those risks that we have just been talking about.

Dr. Procop.

Dr. Procop: Yeah. Thanks. Gary Procop, American Board of Pathology. So these tests are particularly susceptible to pre-analytic variations. And the companies currently do a great job on laying out exactly how the specimen should be drawn, how the specimen should be processed, etc. If those aren't done right, those lead to your indeterminate results, etc. So, in addition to appropriate patient population, which I agree with completely, is all of the pre-analytics that are currently in place, we would want to see those pre-analytics held to that same degree of stringency with the downgrade. So I'm supportive of the downgrade, but we've got to keep that high level of pre-analytic stringency. That's all. Thank you.

Dr. Van Der Pol: Anyone else have any mitigation or special controls that they'd like to see help with the topics we've just discussed? I wonder too if in the assays, maybe we should be encouraging manufacturers to describe results as invalid rather than equivocal, because they really are not interpretable for a clinician. And so even though the test generated a result, the result is meaningless. And so wouldn't an invalid mean more so that somebody wouldn't do what you just described, which is a little bit of a nightmare?

Dr. Kotton, go ahead.

Dr. Kotton: I think invalid would be great terminology because that's really descriptive. That's not borderline. It's just invalid. That's more crisp.

Dr. Van Der Pol: Or uninterpretable, something.

Dr. Kotton: Yeah. Something. Those are much clearer. As far as mitigation, I'll just describe what I do. So I see everyone who's undergoing organ transplant at Mass General in a pre-transplant eval. So I see almost everybody. So it's hundreds of patients a year who are going to undergo immunosuppression, and we have a pretty significant international population, so we have a lot of latent TB. So I see a lot of people that when I eyeball them, they have a lot of TB risk factors. And sometimes one test is negative, but they have a lot of old granulomas or just like a huge history or

whatever. And then I actually use the opposite test. So, I switch between T-SPOT and QuantiFERON. I don't think that the FDA would want to get into the business of recommending that, but that is a mitigation strategy that I personally use. I used to use skin testing, but, again, I've moved away from it. And after the pandemic with virtual visits, it's impossible to do. I don't know if other people have comments on that as a mitigation approach. I do, I always say that I take the positive test. Like, if I have two tests that are contradictory, then I round up, especially in the setting of risk factors. If somebody has zero risk factors, usually they haven't taken a detailed enough history to elicit the risk factors, but that's just what I use as a mitigation strategy.

Dr. Van Der Pol: But that's not uncommon. I mean, we see that even with HIV, not with negative results, but with positive results, where we say that you need to confirm this with a different assay. So I don't see that that's a limitation that's unusual. In this case it would be negatives maybe. If sufficient clinical factors dictate and you get a negative result, you should consider retesting with a different assay. I mean, I don't see why that couldn't be a labeling thing.

Dr. La Hoz.

Dr. La Hoz: We have a similar situation as Dr. Kotton here in Texas with a large proportion of transplant candidates that are born in Africa or Central America and South America. And I guess there's different ways in which this could be approached, but, again, it's not a limitation of the test, per se, but I think about the pretest probability. For example, I was born in Peru, and that is the country with the highest incidents of TB in Central and South America, at least when I used to practice there. And if somebody is born there, probably 90% of the population has laboratory evidence of LTBI. So even with a negative test, I may decide to treat them for latent tuberculosis prior to transplant. Another scenario is that there are calculators where it actually factors race factors, age specific, states within different countries that have high density, X-ray findings, and so forth to calculate what is the post-test probability of a positive test like this or a negative one.

And I factor all that in to decide whether I will test or treat for latent TB, despite the test being negative, in particular in a transplant patient where the risk of developing active TB could be up to 50 times higher than that of the regular population.

Dr. Van Der Pol: Thank you. Dr. Petti.

Dr. Petti: Cathy Petti, Health Spring Global. I agree with Dr. Kotton and Dr. La Hoz. I also want to caution all of us when we're not dealing with immunocompromised hosts, many times these IGRA tests are being used as screening tests in extremely low risk populations. They come across as positive. You do an exhaustive history. You can't even elicit, yeah, I was standing in line in Disney world for six hours and someone was coughing behind me, and then you repeat the test within the same class, meaning another QuantiFERON, for example, and then it's negative. So perhaps in the labeling, we wouldn't necessarily be so prescriptive that it would have to be a different QuantiFERON versus T-SPOT, but certainly important to consider. But on the other hand, I've just had patients that have flipped back. It can be a mess in the general population, I guess is what I'm saying. So in the appropriate clinical context, once again, needs to be emphasized, and confirmation by the same or another method could be perhaps a mitigation strategy in labeling.

Dr. Van Der Pol: So I just want to make sure I'm hearing correctly, but in some populations, based on a risk assessment, negative results would need to be confirmed, while in other populations, because, again, of a low risk assessment, positive results would be. Am I getting that correctly?

Dr. La Hoz: Yeah. I guess the way that I think about this is that if the pre-test probability of latent TB was exceedingly high and you have a negative test, I'm not sure that the second negative test is going to take you to a post-test probability of one percent if you started with a pre-test probability of 90. In the opposite case, if you start with a pre-test probability of 0.0001, even the positive test is not going to take you, with even a pretty reasonable positive likelihood ratio, is not

going to take you to a post-test where it's going to even approach one percent. So I'm not sure that in either extreme, repeating the test is necessary. It just needs to be contextualized that depending on the risk of the population, a positive test doesn't equal disease, and a negative test doesn't equal no disease. It's just a math issue of pre-test diagnostic performance and then post-test problem.

Dr. Van Der Pol: So should we say something more like, without including positives or negatives, but consider re-test based on pre-test positive probabilities? Yes? No? I lost Dr. La Hoz.

Dr. Precop: It's just pre-test probabilities, because it could be negative or positive.

Dr. Van Der Pol: Right. That's what I'm saying. Yeah.

Dr. Precop: Yeah.

Dr. Van Der Pol: Pre-test.

Dr. La Hoz: I guess implicit in that is I'm not sure that also a second test is necessary if really you start with a low pre-test, even if the test is positive, you just say, Okay. Well, we're going to stop there. Additional tests are not going to take us to a place where we're going to make this a high post-test probability of latent TB, and the other way around with the NICT. So what I'm saying is I'm not sure that the additional testing is necessary in every single scenario. There will be some in which it may, but not in all of them.

Dr. Van Der Pol: Right, which is why the word consider, I think, would be important. But regardless, you'll correct me if I don't capture it when we get to the end.

Dr. Moore.

Dr. Moore: Yeah. Well, in thinking about this, I'm in a state with a large rural population, and most of the TB tests that are done, that is the IGRAs that are done, are done by non-physicians, are done in terms of employee health or other work-related issues, educational systems. And so I get this, when they're negative, I don't get the calls; but when they're indeterminate, I get the calls. And very often, they've already been repeated. I guess my recommendation regarding Dr. La Hoz's

statement is, I concur with what he says that my view would be to try to discourage, as much as possible, re-testing and really sort of leave that out of the discussion other than to say consider it for patients who have a high pre-test probability, who have a negative test or an indeterminate test, and then additional investigation may be worthwhile, or something to that point.

Dr. Van Der Pol: I guess the reason I keep bringing this back up is, is this something we feel like there could be a mitigation put into labeling or in the limitations section of a package insert such that it was more clear to clinicians how to act based on these test results, or do we feel like there's not enough information? Because I think that's part of the piece that will drive whether this can be changed from a Class III to a Class II is if we feel like there's enough information to create the right limitations and/or labeling or special controls. So think about that, and we'll come back to each of you as needed.

Dr. Kotton.

Dr. Kotton: I think Dr. Moore's points are really well taken. I don't want to create a situation where we're routinely recommending it. I just meant in like maybe one percent of the patients I see, do I use additional testing. So I didn't mean to open a can of worms. I'm going to put into the chat, there's this great online tool, this TB calculator. I don't know how many people have used that, and I don't know that the FDA would be in the position of recommending use of this, but it is brilliant. And for risk mitigation, this has been super helpful in my clinical use. It's also something that helps a lot with patients to buy in because many patients don't believe in QuantiFERON results. Like they say, oh yeah, I had a BCG when I was one year-old or 65 years ago, or whatever. So it helps a lot with overall understanding, and I think helps with this mitigation. I don't know.

Dr. Van Der Pol: And that's showing up in the chat for anybody who would like to click on that. Okay. Dr. Gerald.

Dr. Gerald: Yeah. Okay. There were a few things, and I'm trying to make sure that I get back to all of them. So I will say that the tests that are approved now do have statements to the effect about the potential for false positive and false negative results and how, even in the intended use statements, they really are only supposed to be used in conjunction with these other history and other test results. The other thing that I will mention is that I think some of the conversation is probably a little bit beyond what we would put into the individual label of a specific test. So for a manufacturer that has decided to have an indeterminate or borderline result, then they clearly need to have very explicit instructions on what someone should be doing, whether it's retesting, how you retest.

But then once you start getting larger than that, in terms of like your clinical algorithm of what other things you should specifically be going to next, because, as it's been discussed, it's going to differ with your population, with your pre-test probability, exactly what would be your next step. That's kind of more outside of our realm and more in the larger professional society guidelines and ideas that say this kind of broader picture of how you deal with these tests in general. Versus I think where our labeling would be more specifically to address things that we've observed for the validation of that individual test. I mean, there are some general things, but I think more general than some of the discussion that we've been having.

And then lastly, which is, I think, really beyond the scope of this discussion today, when we talk about these indeterminate, borderline, equivocal results, it is something that we have a conversation with sponsors about, but the idea is that there is a category where it is a valid result. It still provides some information, right? So, when we know, for example, in these IGRAs some percentage of these indeterminate results are because the sample was mishandled. So, this person could be positive and the sample was mishandled, and it's like indeterminate. So I think we can always have the discussion with the sponsor. It should just be a straight qualitative, and these

should be invalid, but there's still, it doesn't take away the impetus for them to include this sort of category in some circumstances. But we definitely do suggest they have more simple interpretations when they can. I think that was everything that I wanted to comment on.

Dr. Van Der Pol: Dr. Wentzensen.

Dr. Wentzensen: Yeah. I just wanted to mention because some of the discussions here remind me of what we have currently in the cervical cancer prevention arena where we're very engaged in guidelines development, and recently there were new technologies approved by the FDA where the statements really were like according to clinical recommendations or clinical guidelines. And then these guidelines developed by 20 or more clinical societies across the US then give all these detailed recommendations on how to use these tests because there are a lot more applications in the screening and management realm than anything that could be covered in the indication. So, I think that there are many examples there's a very focused indication, but then a reference to clinical guidance that can then really expand on that and can have a lot of these discussions that we just had. And I think that that works pretty well in some areas.

Dr. Van Der Pol: Dr. Beavis.

Dr. Beavis: Yeah. So, I don't know that this is entirely on topic, but I've just got to say, as a pathologist, to hear that we're testing somebody who is a low pre-test probability, and we're going to ignore a positive result if we get it. Sorry, but I think all the pathologists in the group are just sort of nodding. You know, why are we doing the testing? And screening in the United States is generally a low prevalence group. A lot of the screening that used to happen, I used to be screened every year, but those recommendations have backed off. So we have a test that's not 100 percent precise, just given the requirements of handling, given the nature that it's requiring cells to produce things in response to something. And so we're using a test that's very different from some of the other tests that we've talked about today in the context of a low prevalence in the US. And so I just

want to caution the group. We can't be looking for perfection here. The circumstances are just very different, both with the kind of test and the prevalence in the United States.

Dr. Van Der Pol: Other points that people would like to make about potential mitigation strategies or special controls?

Dr. Ng.

Dr. Ng: Yeah. Thank you. I want to jump on Dr. Beavis's band wagon. I do agree with everything she stated. I also separately want to make a comment. To a laboratorian, invalid and indeterminate are different things.

Dr. Van Der Pol: They are.

Dr. Ng: Yeah. Yeah. Yeah. So I understand the clinicians here not knowing how to use indeterminate, but I would really caution against substituting invalid for that. They're quite different. Thank you.

Dr. Van Der Pol: And I think, as I thought about it, I thought uninterpretable might be better because ultimately they really are uninterpretable. Regardless, I think that maybe it's time that we all sit down, both laboratorians and clinicians, and think about what language we've used historically and what language we should use going forward that clarifies things. But that's probably beyond the scope of this meeting. So have we covered all the topics that people think are potential mitigation strategies?

Seeing Dr. Beavis, one more.

Dr. Beavis: Yeah, sorry. And just to clarify for what Dr. Ng was saying, perhaps in the package insert could be explanations for what indeterminate means, the couple reasons that could cause that kind of result, whether it's specimen handling, whether it's something in the nature of the specimen itself, the patient specimen, what are the different reasons? And I think that could help in the interpretation of that result.

Dr. Van Der Pol: Yeah. I think that's possibly true. Okay. I'm going to try to summarize.

Oh, Dr. Kotton.

Dr. Kotton: Thanks to Dr. Beavis for that comment. The problem is nobody reads. I mean, on a clinical level, am I allowed to say on this call, nobody reads the package inserts? So I love a package insert personally. I have a whole bunch. I have many dozens of PDFs, but that's a real issue. I mean, part of what to me is one of the biggest issues here, and it's true with like 1,3-beta-D-glucan and galactomannan testing and all kinds of things, clinicians just want the answer. They don't want to have to talk to the patient, take a history, interact, they just want the test. Is it positive or negative? And for me, that's been a real philosophy change as we've moved towards computer-based medicine. So I'm not mitigating anything. I'm just saying for me it's actually really problematic and is part of the whole situation. I think when we talk about including it in the package insert, if there's a way for computers to actually tell the clinician more of an answer, that would be risk mitigation. What does indeterminate mean, or what does a negative test mean?

Dr. Van Der Pol: And, of course, there is a way. And so we can, as laboratorians, put that in the results so that people see that. And I think that, you know, it just depends on, we try to keep the results streamlined because people then tell us that there's too much language on there, and I just want yes, no. So we can't win. It doesn't matter.

Dr. Kotton: Yeah.

Dr. Van Der Pol: Dr. Ng.

Dr. Ng: Thank you. I just want to emphasize, yes, we hard code the interpretation link to the result, and I think we only have like 100-character limit, so we get our best editor to take that paragraph to still it down to 10 words with no more than two syllables.

Dr. Van Der Pol: It's like writing an informed consent, isn't it? So, can we get to the sixth grade level? Well, all right. So with all that, I'm going to try to summarize.

This one's been a really interesting conversation. And I think that because it is a slightly different type of test, and I think in part because it's an indirect test, I think that that puts our thinking caps on a little bit differently. We talked about one of the things that I wrote down that I think, even though we didn't come back to the specific language here, I still think it comes back to there probably needs to be some sort of labeling or limitation that includes what can go wrong if the pre-analytical steps are not accurately followed. Because I do think that that is one of the reasons you do get those indeterminants or whatever word it is with that particular assay. We talked about having labeling and limitations that were sort of specific to populations, whether that be populations with active TB populations that are immunocompromised or populations that had low pre-test probability or high pre-test probability. And so that's something to think about, but I have to say that amongst the panel, we did not actually ever achieve consensus on what we thought that labeling should be. And so we're not being very helpful to the agency in terms of making a recommendation about that, but just something I think that we've clearly identified a point that we think is a point of weakness that needs to be addressed at some point. And I think that there were no real calls for stringency any different from the Class III level of stringency for sensitivity and specificity, but that we have enough data to understand how the assays that currently are marketed as Class III assays are working, and we think that those performance characteristics are useful clinically. And so if we have special controls that use that same sort of range of sensitivity and specificity, that will probably meet the needs of providers.

Everybody okay with that? Anything I left out. Okay. So now we can go on. Oh, Dr. Stenzel, did you have any additional things that you need to clarify?

Dr. Stenzel: Thanks again to the panel and you. No follow-up questions, but one follow-up comment to Dr. Kotton. I really appreciate that you read the IFU package insert. We spent a lot of

time on that, and there is so much incredible information in it. So thank you for that positive comment.

Dr. Kotton: I would like to say that I often have the package insert in lectures I give. Like I copy and paste it with some art, so I am an aficionado. I think this is a safe space to acknowledge how much I love the package inserts.

Dr. Stenzel: You're an honorary FDA member.

Dr. Van Der Pol: It is nice to hear that. It is nice to hear that. Yes. So it's very funny. Okay. I think we can go on to question three.

Question Three

Dr. Van Der Pol: And question three is essentially the panel deciding if we have opinions about whether this product and other assays, not the specific product, but this type of assay, could be reclassified from Class III to Class II based on the information we have currently about what the risks and mitigations are that could be applied to these types of assays.

So with that, I'll open it up for discussion. Does anyone feel that we don't have enough information to reclassify these? Let's start with the negative stuff. I saw a hand up, and it went away. Dr. La Hoz, did you have a comment?

Dr. La Hoz: Oh, no, but now that you're saying --

Dr. Van Der Pol: It's fine. We gave everybody a chance to be negative. We can give you the first stab at positive.

Dr. La Hoz: I think, based on the current data, I will be supportive of down-classifying.

Dr. Van Der Pol: Dr. Pereira.

Dr. Pereira: Yeah, Marcus Pereira here. I agree. I would support moving to Class II.

Dr. Van Der Pol: Dr. Moore.

Dr. Moore: Yeah. I also agree, level II with special qualifications would be the way to do it. I mean, we really don't want to lose the assays, which are critically important, even though their use and interpretation is often nebulous.

Dr. Van Der Pol: Thank you for that. Dr. Kotton.

Dr. Kotton: I also agree with downgrading to a II.

Dr. Van Der Pol: Dr. Wentzensen.

Dr. Wentzensen: I agree with moving to Class II, and I think there's a great opportunity to develop like parallel recommendations from the clinical community.

Dr. Van Der Pol: Dr. Moore. Did I skip you, or is your hand just still up?

Dr. Moore: Sorry. Left my hand up. Thanks.

Dr. Van Der Pol: Okay. Mr. Spring.

Mr. Spring: Yes. I also agree with the reduced classification of Class II and, at a prior company, will add that we made a decision not to pursue such a test because of the barriers that Tim talked about earlier. So, again, I agree with the down classification.

Dr. Van Der Pol: Dr. Caliendo.

Dr. Caliendo: Angie Caliendo, Brown. Yes, I also agree with down-classification.

Dr. Van Der Pol: Thank you. Dr. Stenzel, your hand is up.

Dr. Stenzel: Yeah, a couple of comments were made about being worried about losing somebody, any of the tests on the market. I didn't want to scare anybody. I don't have no knowledge that there is any risk of losing even one of the two tests. I just brought it up that there is value in down-classification, other than getting more tests on the market potentially. Thank you.

Dr. Van Der Pol: Thank you. Dr. Ng.

Dr. Ng: I agree. Thumbs up.

Dr. Van Der Pol: Dr. Blumberg.

Dr. Blumberg: Agree. This is a little tougher just because there are fewer standards to compare to, but more urgent to do it, I think, because of that.

Dr. Van Der Pol: Dr. Beavis.

Dr. Beavis: I agree.

Dr. Van Der Pol: Dr. Walker.

Dr. Walker: Dr. Walker. I agree.

Dr. Van Der Pol: Ms. Schwartzott.

Ms. Schwartzott: I agree, and I'm hoping that with this reclassification, it'll bring new people to the table that might be able to solve some of the issues that we have with the current tests.

Dr. Van Der Pol: Perfect. Dr. Petti, it looks like you get the last word.

Dr. Petti: Cathy Petti, Health Spring Global. Yes, I agree.

Dr. Van Der Pol: Okay. I will sum this up for you. The panel is in overwhelming agreement that these types of tests should be considered for down-classification from Class III to Class II and that we have sufficient data for you to take action on moving that forward.

Dr. Stenzel, did you need any more information from the panel on this topic?

Dr. Stenzel: No. Thanks for asking, and thanks to you.

Dr. Van Der Pol: Wait. I have a script, and I have forgotten entirely. Okay.

Okay. At this time, the panel is going to hear summations, comments, or clarifications from the FDA. Oh, wait. Sorry. I have to go back to customer comments. I apologize for this. I got too comfortable with what we're doing.

Okay. At this time, I would like to ask our representatives, Dr. Roblena Walker, our consumer representative, Mr. Bradford Spring, our industry representative, and Ms. Jennifer Schwartzott, our patient representative, if they have additional comments about any of the three topics that we have covered today. I'd like to start with Dr. Walker.

Closing Comments

Dr. Walker: Hi. Dr. Roblena Walker, consumer representative. I don't have anything extra to add. I am in agreement with every thought and sentiment that has been shared from my panel members. Thank you.

Dr. Van Der Pol: Thank you. Mr. Springer.

Mr. Spring: Yes. Brad Spring.

Dr. Van Der Pol: Spring. Sorry.

Mr. Spring: That's okay. It's been happening for my entire life. No, I completely agree with all the panelists' comments and the decisions that were made today, or the recommendations I should say. I have nothing else to add.

Dr. Van Der Pol: Thank you. Ms. Schwartzott.

Ms. Schwartzott: I also agree with what everybody has been saying. The more options we have, the better, the more we can get care to the patients. Thank you.

Dr. Van Der Pol: Thank you. So now we will go to summations, comments, or clarifications from the FDA. Dr. Stenzel, you have ten minutes.

FDA Summation

Dr. Stenzel: No worries. I don't think I'm going to take ten minutes. This has been a highly productive, very engaging, very robust discussion today. And, from our point of view, we're very grateful for all of this. To summarize, except for the hepatitis B surface antigen quantification, we have, I think, solid support, sometimes unanimous, for down-classification from Class II to Class III. So thank you for your contributions today.

Adjournment

Dr. Van Der Pol: And with that, I would like to thank the panel, the FDA, and all of the open public hearing speakers for their contributions to today's panel. We will meet again tomorrow starting half an hour later, just to make sure your clocks are appropriate. So, with that, this meeting of the Microbiology Devices Panel is now adjourned. Thank you, everyone.