Food and Drug Administration (FDA)

Center for Biologics Evaluation and Research (CBER)

123rd Blood Products Advisory Committee (BPAC) Meeting

OPEN SESSION

Zoom Video Conference

December 8, 2022

This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

Participants

Chair	Zbigniew "Ziggy" Szczepiorkowski, M.D., PhD, F.C.A.P.	Dartmouth's Geisel School of Medicine	Lebanon, NH
Members	Adaora Adimora, M.D., M.P.H.	University of North Carolina at Chapel Hill	Chapel Hill, NC
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	Sridhar Basavaraju, M.D., F.A.C.E.P.	Division of Healthcare Quality Promotion, CDC	Atlanta, GA
	Evan Bloch, M.D., M.S.	Johns Hopkins University School of Medicine	Baltimore, MD
	Melissa A. Cumming, M.S., CIC	Bureau of Infectious Diseases and Laboratory Sciences	Jamacia Plain, MA
	Brenda J. Grossman M.D., M.P.H.	Barnes-Jewish Hospital, Washington University School of Medicine	St. Louis, MO
	Frank Maldarelli, M.D., Ph.D.	Clinical Retrovirology Section, NIH	Fort Detrick, MD
	Marissa B. Marques, M.D.	The University of Alabama at Birmingham	Birmingham, AL
	Elena Perez, M.D., Ph.D., F.A.A.A.A.I.	Allergy Associates of the Palm Beaches	North Palm Beach, FL
	Richard Scanlan, M.D.	Oregon Health & Science University	Portland, OR
	Kenneth Sherman, M.D., Ph.D.	University of Cincinnati College of Medicine	Cincinnati, OH
	Abdus Wahed, Ph.D.	University of Pittsburgh, Department of Biostatistics	Pittsburgh, PA
Consumer Representative	Susan U. Lattimore, RN, M.P.H.	The Hemophilia Center, Institute on Development and Disability	Portland, OR
Industry Representative	Susan N. Rossmann, M.D., Ph.D.	Gulf Coast Regional Blood Center	Houston, TX
FDA Presenters	Monica (Burts) Young, Ph.D.	Senior Advisor to the Associate Director for Science	CBER
	C.D. Atreya, Ph.D.	Associate Director for Research, Office of Blood Research and Review	OBRR, CBER
	Hira Nakhasi, Ph.D.	Director, Division of Emerging and Transmitted Diseases	DETTD, OBRR, CBER
	Sanjai Kumar, Ph.D.	Chief, Laboratory of Emerging Pathogens (LEP)	DETTD, OBRR, CBER
	Indira K. Hewlett, Ph.D.	Chief, Laboratory of Molecular Virology (LMV)	DETTD, OBRR, CBER

FDA Staff	Peter W. Marks, M.D., Ph.D.	Director	CBER
	Nicole Verdun, M.D.	Director, Office of Blood Research and Review	OBRR, CBER
	Anne Eder, M.D., Ph.D.	Deputy Director, Office of Blood Research and Review	OBRR, CBER
	Peyton (John) Hobson, Ph.D.	Deputy Director, Division of Emerging and Transfusion Transmitted Diseases	DETTD, OBRR, CBER
	Prabhakara Atreya, Ph.D.	Director, Division of Scientific Advisors & Consultants	CBER
	Christina Vert, M.S.	Designated Federal Officer (DFO), Division of Scientific Advisors & Consultants	CBER
	Sussan Paydar, Ph.D.	Backup DFO, Division of Scientific Advisors & Consultants	CBER
	LaShawn Marks	Committee Management Officer, Division of Scientific Advisors & Consultants	CBER
	JoAnne Lipkind	Committee Management Officer, Division of Scientific Advisors & Consultants	CBER
	Tonica Burke	Committee Management Specialist, Division of Scientific Advisors & Consultants	CBER
Open Public Hearing Speakers	Dominika Misztela, Ph.D.	Head, Global Regulatory Policy, Plasma Protein Therapeutics Association	Brussels, Belgium
	Cole Williams	Founder, Pride and Plasma	

Table of Contents

Page

Opening Remarks: Call to Order and Welcome

Dr. Zbigniew Szczepiorkowski (Ziggy): Good morning, everyone. It is my pleasure to open the 123rd meeting of the Blood Products Advisory Committee. I would like to welcome all who will be participating in today's meeting, the BPAC members, as well as our participants from FDA, and anyone from the public who may be viewing this remotely. My name is Zbigniew Szczepiorkowski, and I have the privilege to serve as a new chair of this committee. As my last name is rather complex. I prefer to be called Ziggy, but understand that for some it would be easier to call me Doctor Ziggy. I'm a Professor of Pathology and Laboratory Medicine and Professor of Medicine at Dartmouth Geisel School of Medicine in Hanover, New Hampshire.

I would like to express my gratitude to Dr. Richard Kaufman for serving as the chair of the BPAC over his recently concluded term. As we continue our meetings over the virtual platform, I would just like to remind the committee members and participants to use the Raise Your Hand feature on the system if you have a question or comment to make so I can call on you to speak. Today, we'll be reviewing two research programs that take place within CBER. These are the research programs of the Laboratory of Emerging Pathogens, LEP, and the Laboratory of Molecular Virology, LMV, both in the Division of Emerging and Transfusion Transmitted Diseases, Office of Blood Research and Review, Center for Biologics Evaluation and Research.

FDA is tasked with regulating a wide range of different biomedical activities that are always changing and advancing, and to complement the regulatory work that they do, various offices within CBER, making basic and translational research programs that are meant to align with their regulatory mission, as well as to lead scientific developments. Research programs, and

progress of the Laboratory of Emerging Pathogens and Laboratory of Molecular Virology underwent a detailed external review earlier in the year, and our committee will be reviewing the report prepared by the reviewers, led by Dr. Brenda Grossman. We'll discuss this report in a closed session later today. At this point, I would like to hand the meeting over to Christina Vert for administrative announcements, roll call, and conflict of interest statements.

Administrative Announcements, Roll Call, and Conflict of Interest Statement

Ms. Christina Vert: Good morning, everyone. This is Christina Vert, and it is my great honor to serve as a Designated Federal Officer, DFO, for today's 123rd Blood Products Advisory Committee Meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research, and the Committee, I am happy to welcome everyone for today's virtual meeting. Today, the committee will meet an open session to hear an overview of research programs of the Laboratory of Emerging Pathogens and Laboratory of Molecular Virology in the Division of Emerging and Transfusion Transmitted Diseases, Office of Blood Research Review, Center for Biologics Evaluation and Research. Today's meeting and topic were announced in the Federal Register Notice that was published on October 18th, 2022. Next slide.

At this time, I would like to introduce acknowledge outstanding leadership of my Division Director, Dr. Atreya, and excellent work of my team, whose contributions have been critical for preparing for today's meeting. Along with Dr. Atreya, Dr. Sussan Paydar is my backup DFO and will be supporting me throughout the meeting today. Staff within BPAC who contributed significantly and provided excellent administrative support are: Ms. Tonica Burke, Ms. Karen Thomas, Ms. Joanne Lipkind, and Ms. Lashawn Marks. And I would also like to

express my sincere appreciation to Mr. Derek Bonner and Ms. Gretchen Carter in facilitating the meeting today. Also, our sincere gratitude goes to many CBER and FDA staff working behind scenes trying to ensure that today's virtual meeting will also be a successful one, like the previous BPAC meetings. Please direct any press media questions for today's meeting to FDA's Office of Media Affairs at FDAOMA@FDA.hhs.gov. The transcriptionist for today's meeting is being provided by Translational Excellence. Next slide.

We will begin today's meeting by taking a formal roll call for the Committee members. When it, it's your turn, please turn on your video camera, unmute your phone or audio, and then state your first and last name. And when finished, you can turn off your camera and mute so we can proceed to the next person. Please see the memo roster slides, in which we will begin with the chair. Dr. Ziggy?

Dr. Ziggy: Zbigniew Szczepiorkowski, present.

Ms. Vert: Thank you. Dr. Adimora.

Dr. Adimora: Adaora Adimora, present.

Ms. Vert: Thank you. Dr. Ballow.

Dr. Ballow: Morning. I am present.

Ms. Vert: Thank you. Dr. Basavaraju.

Dr. Basavaraju: Hi. Good morning. I'm present as well.

Ms. Vert: Thank you. Next slide. Dr. Bloch.

Dr. Bloch: Evan Block present.

Ms. Vert: Thank you. Melissa Cumming.

Ms. Cumming: Good morning, Melissa Cumming, present.

Ms. Vert: Thank you. Dr. Grossman.

Dr. Grossman: Brenda Grossman, present.

Ms. Vert: Thank you. Susan Lattimore.

Ms. Lattimore: Good morning, Susan Lattimore, present.

Ms. Vert: Thank you. Next slide. Dr. Maldarelli.

Dr. Maldarelli: Good morning, Frank Maldarelli, present.

Ms. Vert: Thank you. Dr. Marques.

Dr. Marques: Good morning, Marissa Marques, present.

Ms. Vert: Thank you. Dr. Perez.

Dr. Perez: Good morning, Dr. Perez. Present. Thank you.

Ms. Vert: Thank you. Susan Rossmann.

Dr. Rossman: Good morning, Susan Rossman.

Ms. Vert: Thank you. Next slide. Dr. Scanlan.

Dr. Scanlan: I'm Richard Scanlan. Present.

Ms. Vert: Dr. Sherman.

Dr. Sherman: Ken Sherman, present.

Ms. Vert: Thank you. Dr. Wahed.

Dr. Wahed: Present. I go by Wahed, so you can just call me. Yeah.

Ms. Vert: Wahed, sorry. Thank you. Okay. We have a total of 15 members, 14 voting and one non-voting member. Next slide. I would now like to acknowledge the leadership and management, including Dr. Marks, Dr. Verdun, Dr. Eder, Dr. Chintamani Atreya, Dr. Nakhasi, Dr. Hobson, Dr. Hewlett, Dr. Kumar, and Dr. Young, some of whom will be joining the meeting later today, and others who will be providing overview presentations shortly. Next slide.

Before I begin with the reading of the Conflict of Interest statement, I would just like to briefly mention a few housekeeping items related to today's virtual meeting format. For members, speakers, FDA staff, and anyone else joining us in the Zoom room, please keep yourself on mute unless you are speaking to minimize feedback. If you have raised your hand and are called upon to speak by the Chair, please state your name, speak fully and clearly, so that your comments are accurately recorded for transcription and captioning. Thank you.

Now I will proceed with reading the FDA Conflict of Interest Disclosure Statement for the public record.

Welcome to the December 8th, 2022 meeting of the Blood Products Advisory Committee. The Food and Drug Administration is convening virtually today, December 8th, 2022, for the 123rd meeting of the Blood Products Advisory Committee, BPAC, under the authority of the Federal Advisory Committee Act, FACA, of 1972. BPAC Committee will meet an open session to hear an overview and update of the research programs of the Laboratory of Emerging Pathogens and the Laboratory of Molecular Virology within the Division of Emerging and Transfusion Transmitted Diseases, Office of Blood Research and Review, Center for Biologics Evaluation and Research.

For agency guidance, these topics are determined to be non-particular matters, which have no impact on outside financial interests. Hence, no effective firms are identified, and members are not screened for this topic. After the open session, the meeting will be closed to the public for Committee deliberations. Today's meeting will have a closed session from 12:35 PM to 1:30 PM to permit discussions where disclosure would constitute a clearly unwarranted invasion of personal privacy, (5 U.S.C. 552b(c)6)). Dr. Ziggy is serving as the Chair for both the open and closed sessions for this meeting.

The following information on the status of this advisory committee's compliance with federal ethics and conflict of interest laws, including but not limited to 18 U.S. Code§208 is being provided to participants at this meeting and to the public. With the exception of the industry representative, all participants of the Committee are either special government employees or regular federal government employees from other agencies and are subject to the federal conflict of interest laws and regulations. Given that the topic of this meeting is determined to be non-particular matters, it has also been determined that the overview and updates of this meeting present no actual or appearances of financial conflict of interest.

Dr. Susan Rossmann is currently serving as the industry representative to this Committee. Dr. Rossmann is employed by the Gulf Coast Regional Blood Center. Industry representatives act on behalf of all related industry and bring general industry perspective to the Committee. Industry representatives are not special government employees and do not vote and do not participate in the closed session.

Ms. Susan Lattimore is serving as a consumer representative. She is employed by the Hemophilia Center, Institute on Development and Disability. Consumer representatives are appointed special government employees and our screens and cleared prior to their participation. They are voting members of the committee, and hence do have voting privileges, and they do participate in the closed session.

FDA encourages all meeting participants, members, or consultants, including Open Public Hearing speakers to advise the DFO and the Committee if they realize they have any financial, professional, or regulatory relationships with any of the topics or individuals being discussed today that were not previously disclosed, and recuse themselves from Committee discussions, and their absence will be noted for the record. This concludes my reading of the

Open Session Conflict of Interest Statement for the public record. At this time, I would like to hand over the meeting to Dr. Ziggy. Thank you.

Dr. Ziggy: Thank you, Christina. Our Next order of meeting, I'd just like to introduce Dr. Monica Young, who is a Senior Advisor to the Associate Director for Science for CBER. Dr. Young, please turn your camera on and unmute. The floor is yours.

Overview of CBER Research Programs

Dr. Young: Good morning, and thank you, Dr. Ziggy. In the next few minutes, I will give an overview of the CBER research program, including how the CBER Research Program is evaluated and how sizes it reports are used. Next slide, please. I'm sure you know by your service on this Committee that CBER regulates a number of complex products, including blood and blood products, cell imaging therapies, tissues, vaccines, fecal microbiota products, and over 400 allergenic products. Next slide, please. CBER has scientists in broad areas of expertise of to cover a variety of topics and challenges that arise when biologics. Next slide please.

Research is a part of the strategic goals, goal number two. So here on this slide are the four main goals of CBER's current strategic plan to support CBER's mission and advance the science spaces of regulation of biologics, human tissues, and blood. Goal two is to conduct biologic research to address challenges in the development and regulatory evaluation of medical products. Next slide, please.

CBER takes a collaborative approach to regulation of biologics, including the review of data submitted by sponsors, internal discussion, post-market surveillance, and active research. The research programs are investigator initiated and range from basic to target studies related to

regulatory products. The research program and its structure help to ensure the understanding of advanced techniques that are the source of data in regulatory submissions and decisions. The research program helps to ensure efficient, effective, and credible review and fosters regulatory decisions based on science. CBER's research and review are integrated. Next slide please.

So what I mean by this is that the regulatory review teams in CBER include a chemistry, manufacturing, and control product reviewer who evaluates aspects of a submission such as the scientific rationale, the data for proof of concept, product production techniques and the resulting product, quality control testing, and clinical assays. Research staff spends substantial amount of time serving on regulatory review teams. Some CMC product reviewers are what we refer to as researcher reviewers. Researcher reviewers review regulatory submissions and lead a research program. Also on a review team are the clinical reviewers who review the clinical trials data and statistical reviewers that help pull it all together. Next slide please.

So in this schematic, we'll demonstrate how science and regulation is used to advance product development. This approach ensures that science is applied throughout the life cycle of and through of the review of a product. This schematic demonstrates how CBER's research programs fill gaps in scientific knowledge and help overcome obstacles in product development. As public health needs arise, novel products are developed, and with these novel products come regulatory challenges. Many of the questions and concerns may include how to best characterize complex products, how best to design non-clinical studies, how to provide predictive assessments of safety and efficacy, and how to overcome potential contamination of biological products. This is where we apply science to developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA regulated products. The discovery of the new tools assists in regulatory policy and decision making, and the outcome of this applied

science provides improved data to assess the benefit to risk ratio of the products, and in many cases, leads to licensure of novel biologics. Next slide, please.

The CBER laboratories are located at the White Oak Headquarters in Silver Spring, Maryland. We have over 450,000 square feet that allows for roughly 150 BSL-1 to BSL-3 laboratories and offices for about 500 research staff. Currently, the CBER core facilities include flow cytometry, and focal and electron microscopy, and high performance integrated virtual environment, which provides the bioinformatics support for next generation sequencing analysis. CBER also has a biotechnology core facility with state-of-the-art instrumentation, as well as the vivarium with BSL-3 capabilities. Next slide, please.

CBER is active in leveraging resources and fostering collaborations. This chart shows the types of formal collaborations that we have in CBER. CBER collaborates nationally, internationally, and across sectors, mostly in academia and with the National Institutes of Health. Next slide, please. This pie graph shows the type of formal external leveraging mechanisms that we use in a given year. Next slide please.

We believe that CBER's research program has several benefits. the research program allows our scientists to prepare for future innovative products and public health challenges, as well as develop tools and data that are available to stakeholders and support the development of all product classes. The research program attracts and maintains highly trained scientists with the necessary expertise to review regulatory submissions, and the studies conducted field knowledge gaps that inform policy development and regulatory decision making. Next slide, please.

The research program is evaluated in several ways. First, we have inner reporting, which is studied yearly by principal investigators. We have peer review of new projects, so that new projects receive additional scrutiny, taken into consideration horizon scanning and immediate

public health needs. We have external review of the research program by experts in the field that are conducted every four years in the format of site visits. And lastly, the Office of Center of Leadership annually evaluate the research program through the inner review of the research program at the project level. In addition, horizon scanning is done by the Offices and our Regulatory Science Council, which is composed of Office Research Directors and Office of Center of Leadership. Next slide, please.

The site visitors are asked to evaluate the research programs based on CBER's evaluation framework. So this includes mission relevance. In general, they're asked to evaluate the alignment of the research program with CBER and with the Center's and Office goals and objectives in mind. We are asked to evaluate dissemination, which includes presentations and publications, as well as impact on the scientific community and regulated stakeholder. And lastly, unique contribution to regulatory practice, which is to evaluate how the scientific outcomes from the research program enhances CBER's regulatory mission. And in recent years, we've developed tools to track the components that make up this evaluation framework. Next slide please.

I'll wrap up with a bit about the site visit report. The site visit review teams are subcommittees of the Advisory Committee. I want to thank the site visit review team chair for your leadership. And this draft report is developed by the site visit team, and it has been distributed to the Advisory Committee. The Advisory Committee is asked to review and evaluate it and either accept the report, amend the report, or reject the report and send it back to the site visit review team. Once the report is approved by the Advisory Committee, the final report is very valuable and is used in many ways: by the PIs for improving their research program, by

their supervisors for the internal review of the program's progress, and by research management, where resource allocation decisions may be impacted by the report. Next slide.

To close, I again want to thank the site visit review team for writing the report and for each of you for evaluating the report. We really do thank you. These site visits do help to maintain the high quality of our research program. We value your insights and your comments. I'm happy to take any questions. Thank you.

Q & A

Dr. Ziggy: Thank you. Dr. Young, for your very informative presentation. I would like to now open the presentation to any questions from the Committee members. If you have questions, please raise your hand on the system, and when called on, turn on your camera and unmute your microphone prior to your question. Thus far I don't see any hands raised. I'll give you a moment for the Committee members to think about anything you would like to ask. Okay. Dr. Young, thank you again very much for your presentation, and we'll move to another point on the agenda. In this case, I would like to introduce our next speaker, Dr. Chintamani Atreya, Associate Director for Research. Dr. Atreya, please turn your camera on and unmute. The floor is yours.

Overview of OBRR and Research Programs

Dr. Atreya: Thank you, Dr. Ziggy. I will provide a brief overview of our office and the research programs. Can I have the next slide please? Okay. So, here you see the structure of our

office, and then we have an office director. We have quality staff and policy staff under the office director. And then we have two divisions. One is the Division of Emerging and Transfusion Transmitted Diseases. In short, we call it DETTD. And this division has one review and two research branches. And the other division is the Division of Blood Components and Devices; we call it DBCD. It has three review and two research branches. Next slide please.

I will give you a little bit more detail of that. And so the structure: Office Director is Nicole Verdun, and then Deputy Director is Ann Eder, and myself as the Associate Director for Research. And then the two divisions, which we are talking about in detail. The DETTD Director is Hira Nakhasi and Deputy Director is John Hobson. And we have two laboratories in such laboratories, there are the Laboratory of Molecular Virology and the Laboratory of Emerging Pathogens. And some of these PIs from these two labs are subjected to the site visit. And that's what you are reviewing today. And the other division is the Division of Blood Components and Devices. The Director is Orieji Illoh, and then Deputy Director is Wendy Paul, and we have two laboratories. One is the Laboratory of Cellular Hematology. The Chief is Jaroslav Vostal, and the other lab is the Laboratory of Biochemistry and Vascular Biology; the Chief is Abdullah Alayash. Next slide, please.

Our office mission is to ensure the safety, efficacy, and availability of blood and blood products through regulation of blood and blood components for transfusion and plasma for fractionation. Devices used in the manufacture of blood and blood components, for example, blood establishment computer systems, automated cell separators, and so on, and blood collection containers and additive solutions. For example, like anticoagulants. And then plasma volume expanders, oxygen carrying solutions, and serological and nucleic acid assays for blood

donor screening and confirmation for transfusion-transmissible agents, and diagnostic tests for human. And devices for the pathogen reduction of blood components. Next slide, please.

To fulfill our mission, we establish policies and standards to assure donor safety and the safety of blood and blood products. And we review applications for investigation and commercial use of blood products, related devices, and retroviral diagnostics. Perform establishment inspections and help the Agency in regulatory compliance actions, perform hazard health hazard evaluations and risk assessments of blood components and blood products. We engage in emergency preparedness. For example, recently everybody knows about the COVID-19 public health emergency, and we engage in global outreach and cooperation, and we organize scientific workshops on timely topics important to our office. And then we also conduct research to facilitate the development, manufacture and evaluation of blood products and retroviral diagnostics. Next slide, please.

So, the vision for research of our Office is to support the FDA initiatives in regulatory science, including medical countermeasures to facilitate product development through focus on scientific questions critical to effective regulation; concentration in areas where our unique role as regulators is most contributory; and provision of an infrastructure for investigation of product limitations and failures; and advancing innovation research areas that enrich FDA's regulatory science base. Next slide, please.

Our office research has two goals, and the goal one is to assess and promote safety and effectiveness of transfusion products and related devices and technologies. Objectives included in this goal are evaluation of *ex vivo* stored platelets and red cells for safety and efficacy; evaluation of safety and effectiveness of oxygen carrying solutions collected like products and related biologics, for example; and the development and evaluation of reference panels for

molecular typing methods for blood groups and HLA antigens; and facilitate development of pathogen reduction technologies applicable to whole blood and blood components. Next slide, please.

Our goal two is to assess and promote safety and effectiveness of Transfusion-Transmitted Infectious Diseases (TTID) agent donor screening and supplemental tests, and retroviral diagnostics. The objectives under this goal are evaluation of screening and confirmatory technologies for detection of transfusion transmitted infectious disease agents for assurance and enhancement of blood safety, development and evaluation of reference panels for screening and confirmatory tests for TTID agents and retroviral diagnostics, and facilitate preparedness for blood safety from emerging infectious agents and other pathogens of domestic and global significance through investigations of mechanisms of transfusion and pathogenesis. Next slide, please.

What are our research resources? We have the following resources to perform our research. Our subject expertise includes biology, virology, bacteriology, parapsychology, prions, cell biology, immunology, biochemistry, and physiology. And our programs are mostly funded by both internal and external sources, such as NIH and CRADAs. And right now we have 15 investigator-initiated programs located in two Divisions under four Laboratories, as it had shown in my second slide. And the next slide, please.

We also perform global outreach. Our staff participates either as a member or observer in WHO initiatives. For example, a Collaborating Center for Biological Standardization, Expert Committee on Biological Standardization, Blood Regulators Network, Prequalification Program for Diagnostics, and European Directorate for the Quality of Medicines and Healthcare, and a Blood Transfusion Sector, International Society for Blood Transfusion Working Groups on

Transfusion Transmitted Diseases, Hemovigilance, and Global Blood Safety, and also FDA/EMA/Health Canada Cluster meetings and events.

Next slide please. So, in conclusion, we believe that research is integral to the mission of OBRR and FDA, and our OBRR research facilitates product evaluation development and is aligned with the regulatory science mission of CBER and FDA. Thank you.

Q & A

Dr. Ziggy: Great presentation. I'm looking at hands, but I don't see any, but I have a privilege of asking a question of my own. And that will be, you have a slide on the mission, the research mission, which I think is very, very important. What's the process for determining what makes into the mission research mission for OBRR? How do you do that and who is involved?

Dr. Atreya: Sure. can you go back to the slide? I think that my third slide or fourth slide. The way we look at is that there's always a kind of a horizon scanning. We look at these things, what is coming up in the next four or five years, and then look at what is feasible that can be done with including what we have, our resources, and the expertise. Based on that, we'll make a decision that this can be a priority for the next few years. That's the way we look at it.

Dr. Ziggy: And to what extent is the influence of the site review, which one of these we will do today, influences your decision for the future four to eight years?

Dr. Atreya: Certainly. The site visit report is very critical, and if the site visit report includes the future that is known, and then if it is not in already in our programs, we certainly include them based on, as I said again, the expertise that are available and also the resources. And if it becomes a really high priority, then we try to also recruit new investigators into the programs.

Dr. Ziggy: Dr. Boas we're know to recognize you, you raise your hand.

Dr. Wahed: So this is a clarifying question. You mentioned that your research is funded through intramural and extramural. Extramural, you mentioned NIH and institutions. Is that, you compete exactly the same way as the other institutions, like academic institutions, compete for these grants?

Dr. Atreya: No. because as a Federal Agency, we cannot compete directly for NIH grants, but normally what happens is we become a collaborator for one of those RON grants or something that so they will be the main PIs and then we provide certain information and certain tools that are available within our reach to collaborate with them. And so we become a collaborator. We do not directly get funding from NIH. But in some rare cases, NIH itself will ask for a kind of an IAA interagency agreement because some work has to be done which cannot be done in other places. Then that specific IAA can be taken. We can say we're from FDA, and we'd get funding from that.

Dr. Ziggy: Thank you for clarifying the question. Any other questions? I don't see any hands raised. Again, Dr. Atreya, thank you so very much for this really excellent presentation.

Dr. Atreya: Thank you, Ziggy.

Dr. Ziggy: The next presentation, the next presenter… I'd like to introduce the next speaker, Dr. Hira Nakhasi, Director of Division of Emerging and Transfusion Transmitted Diseases. Dr. Nakhasi, please turn your camera on and unmute. The floor is yours.

Overview of Research and Regulatory Programs of DETTD

Dr. Nakhasi: Thank you, Dr. Ziggy. And good morning to all of you. My name is here Hira Nakhasi. I am the director of the Division of Emerging Transfusion Transmitted Diseases, where PIs from those two Laboratories of Emerging Pathogens and Laboratory of Molecular Virology were site visited in the beginning of this year. And that site visit report is being reviewed today at this Blood Product Advisory Committee. Next slide, please. So — excuse me, I have a cough so I may be coughing in between. I apologize for that.

So the Division of Emerging Transfusion Transmitted Diseases is organized in the immediate Office of the Director, myself, and the Deputy Director, J. Peyton Hobson, and Associate Deputy Director for Policy, Julie Lathrop.

Then we have organized, as Dr. Atreya mentioned, we have two research laboratories, Laboratory of Molecular Virology and Laboratory of Emerging Pathogens. And the third branch is the Product Review Branch. That third branch is staffed with the full-time reviewers. They do not do any research activities. They review full-time all the applications, which I will explain in a minute. So the laboratory has its PIs and then their staff, which helps them and supports their research programs. The PIs have been identified by the bold letters and their staff is under there and under them. Next slide please.

So the mission of the division of Emerging Transfusion transmitted diseases as Dr. Atreya mentioned earlier, is to ensure blood safety and availability. What do I mean by that? There are about each year, many of you know, about 14 million units are transfused annually. And out of that 10 million are red blood cells, 2 million platelets, and approximately 2.4 million plasma units. Now, risk of transfusion transmitted infections has been reduced with the introduction of the FDA license or clear tests site, which includes both the nucleic acid tests as well as also the serological test.

In some cases, both nucleic acid as well as serological tests are used to confirm the infection or absence of infection in these units. And in some cases, only the serological assays are used, such as T. *cruzi*, syphilis, CMV, HTLV. And until now, until a few years back, we were also testing for Zika virus. Since the incidence of Zika virus has gone significantly low and almost not found any cases, we took a policy decision to stop testing for the Zika virus under nucleic testing. Next slide please.

So, the overview of these laboratories. I just wanted to go a little bit deeper into what these focus on. The research program, basically. The Laboratory of Molecular Virology focuses on the pathogenesis of retrovirus. And Laboratory of Emerging Pathogens focuses on emerging and re-emerging blood-borne parasitic viral agents and tick-borne pathogens. And as I mentioned earlier, Product Review Branch focuses on review of regulatory submissions, which are relevant to donor screening assays, diagnostic assays, for HIV. Next slide please.

So, little bit deep dive. And what is the research programs which people in the PIs do in these respective laboratories? So we, these PIs, plan and conduct mission-related research. As question was earlier asked, how do we determine that? First of all, we, as Dr. Atreya mentioned, it's a horizon scanning. And if there is a particular agent which is impacting the blood safety, we would like to understand the pathogenesis of those agents, which have been done time and again, as many of you know on the Committee that we, when the West Nile virus came along, we started program on West Nile.

We also have Dengue virus, Chijungunya Virus. And when Zika came along, we started a program on Zika virus. In addition, we have human retroviruses, HIV-1, HIV-2, and HTLV. Program hepatitis agents, A, B, C, and E, and parasitic agents, *malaria, T. Cruzi, Leishmania*,

and tick-borne agents like babesia. And recently we started also *Anaplasma* and *Ehrlichia* because now cases of those tick-borne diseases are on the rise, at least in the Northeastern region.

We also are continuously working on the bacteria, for example, Treponema pallidum. We have historical research going on the transmissible spongiform encephalopathies Agent, vCJD/CJD, even though the incidence has gone down. We are trying to figure out how to wind down that program.

Then, in addition to that, some of these members of the research group also help to review these applications, along with the full-time regulatory staff. Regulatory to use submissions are like biological license applications, PMAs, 510(k)s, INDs, as well as evaluating these assays in the lab to find out whether those assays and performance of disease are up to the par. We also develop policies and guidance documents for blood donor screening tests and retroviral diagnostics. Next slide, please.

In addition, we also make, because these assays have to be evaluated before they are released to the market, and we have now started — earlier, we used to develop these later release panels, which is important for the release of this thing. But we have transferred that activity to our sister office, Office of Compliance, but we continue to provide the source materials because scientists, our PIs, know what is really the material we need to test, and therefore they provide those materials to the OCBQ. And those laboratories in there, they will help to provide these lateral talents.

In addition, we provide scientific and technical advice to other agencies, government components such as CDC, DOD, and different Department of Human Health Services. In addition, we also have outreach to stakeholders, such as today's Blood Products Advisory Committee meeting, where if there are issues with particular agent, we come to the Committee

and seek their advice. We also participate in the Department's Advisory Committee on Blood, Organ and Tissue Safety Availability. We serve as liaisons to blood establishments and device manufacturers such as AABB, PPTA, and sometimes Aramed. We also, as Dr. Atreya mentioned, we collaborate with and WHO as a collaborating center for IVDs, in vitro diagnostic tests. And we provide significant input. And sometimes when they have to validate some of these standards, our laboratories participate in that. We also participate in horizon scanning of emerging and reemerging bloodborne pathogens as a part of the PHS subcommittee of Emerging Infectious Diseases with CDC, NIH, and other components of the Department of Human Health Services. Next slide, please.

Now, because this is a research program evaluation, I wanted to highlight some of the select examples of recent, last year's publication. And these many publications are varied in world journals, other journals. And these are very high impact journals which contribute to the, not only to the mission, but also the advancing the field in particular areas. I don't want to keep on seeing each list here, but I just wanted to give you a flavor of some of these publications, which have been published in the last one year. Next slide, please.

And same thing. This is another list of publications, which includes not only understanding the pathogenesis, but also developing standards, and also trying to understand the drift of Ebola genome with resequencing microarrays. And developing secondary standards of hepatitis E viruses. So those are the areas, both applied, as well as pathogenesis-related research publications. Next slide, please.

This staff, not only the research reviewers in the two laboratories, but also the Product Review branch. We have in the last one year reviewed approximately more than 400 applications, which is a whole slew of things: BLAs, PMAs, BLA and PMA supplements. We

have licensed several donor screening and cleared HIV diagnostic assays, and in fact, you must have recently and also involved in the policy decisions and policy making. For example, recently you must have seen the FR notice for reclassification of some of these HIV diagnostic and viral load assays to have a least burdensome but appropriate regulatory pathway for that. In the last year, approximately 30 publications from 10 or 11 PIs from the two laboratories, and this all was possible through the, both intramural, mostly intramural and some outside funding from through greater interagency agreements, approximately more than 2 million dollars. Next slide, please.

So I just wanted to highlight the purpose of today's thing will be that, you know, you would have the following these in this slide that shows this PIs, which were site visited earlier, on May 12th, 2022. And their scientific program was evaluated. And those are Indira Hewlett, Luisa Gregori, Gerardo Kaplan, David McGivern, and Maria Rios. And today you will hear the summary of these five programs which were evaluated through their Lab Chief, Dr. Indra Hewlett, who will talk about the Laboratory of Molecular Virology program, which was a site visit. And individual PIs, briefly, what the program was and is. And in the same way Dr. Sanjai Kumar will talk about the research programs of the three staffs, which are reviewed in his branch. So next slide, please.

I want to thank you for your attention and also thank you for your services to evaluate this thing. And I will stop there and take any questions. Thank you very much.

Q & A

Dr. Ziggy: Thank you, Dr. Nakhasi, for your excellent presentation. I'd like to open the presentation to any questions from the Committee members. Again, please raise your hand

and when you call, turn your camera and mute your microphone prior to asking question. I don't see any hands raised. so maybe I'll say…

So maybe again, for my perspective, to learn more about how the system works. Could you, Dr. Nakhasi, asking the following questions. Thee appointments and the researchers, basically 50/50, the evaluation. How do you manage this very big workload? Clearly, you showed in your slides, there's a lot of work being done by the scientists and researchers with their actual research. How do you manage that?

Dr. Nakhasi: Well, you know, that's always a challenge and depends upon… but what we do is that, since we have significant support for each PI, so those support helps the PI, Principal Investigator, to conduct the research and devote some of their time to — whatever it is, 50% time, it can vary depending upon how much workload is there — and to focus on that. So that's really the way to do it. Because it is important to have the support for the PIs. Otherwise if there is no support, then obviously, they may not be able to focus on the research. And as you saw, that having, there is a significant support. It's not as big in the academia — you know, 10, 12 people — minimum two to three people, and sometimes one or two people depending upon the resources available. So that's how we support that. I hope I answered your question.

Dr. Ziggy: Yes, thank you. Dr. Sherman, you have a question?

Dr. Sherman: I do. Thank you. You mentioned scanning the horizon for new threats, new issues. I'm wondering exactly how do you do that? For example, there's been some reports of increasing ortho bunia viruses, like lacrosse, at least regionally in parts of the country. When and how do you decide to incorporate viruses like that into both surveillance and your research agenda?

Dr. Nakhasi: Thank you for asking that question. Yes. The horizon scanning, there are several ways of doing it. One is the researchers also are looking at the literature and also finding what is coming down the pipe. And the important thing is that we have to make sure how that pathogen, whether it's virus, parasite, or bacteria, impacts the blood safety. Is there an asymptomatic phase, because that would cause the blood impact on blood safety. And we also have discussions with the CDC and as I said, Emerging Infectious Diseases subgroup of the Public Health Services. We have monthly or bimonthly or sometimes three, every three months discussions, where we talk about with the other agencies, what they think other things impact the blood safety.

For example, I'll give you an example. Tickborne diseases has been now on the rise for the last several years. We have seen that. And therefore we decided to hhave a program. And we hired a new PI, Dr. Brendan Ellsworth (phonetic), who has expertise in this area. And so that's how we see it. And look at both literatures, and attending the meetings, discussing with our public health partners, and also sometimes with the listening at ABBs and meetings and other meetings where they discuss what is going on. And important thing is to make sure it, how it impacts the blood safety. And so therefore, those are the agents we are selecting. And I gave you an example of you know, tick-borne diseases, which is on the rise. And so we were already looking at the BAA before, now we hear of [indiscernible viruses] and other things are coming up.

So I, I understand, Dr. Sherman that, you know, this is another virus, and we will be looking at it and seeing how much impact it has. And maybe, down the road, we can see if it can be incorporated. And depending upon the resources — we have not unlimited resources. And you know, also it is important that PIs cannot be shifting their focus every two years. Which is

okay with that. But I think the important thing is that we need to determine how much it impact it has on the blood safety. I hope I answered your question.

Dr. Sherman: Thank you.

Dr. Ziggy: Thank you, Dr. Sherman. Any other questions? I don't see any other hands, so thank you so much for the presentation.

Dr. Nakhasi: Thank you, thank you.

Dr. Ziggy: I'll move to the next presentation. I would like to introduce our next speaker, Dr. Sanjai Kumar, Chief of the Laboratory of Emerging Pathogens in CBER. Dr. Kumar, please turn your camera on and unmute. And the floor is yours.

Summary of Viral Diseases Research Programs of LEP

Dr. Kumar: Okay. Good morning, everyone. Thank you, Dr. Ziggy. I hope everyone can see and hear me. I'm going to present somebody of viral disease research programs of liberty of emerging pathogens, and Dr. Nakhasi has given you an overview of the mission of Emerging Pathogens, which we call LEP. Next slide, please.

So, to begin with, the Dr. Kaplan program on Diagnosis and Pathogenesis of Filoviruses, mostly Ebola virus and Hepatitis A virus, with the intent to conduct mission-oriented research in Filoviruses and HAV in support of the safety of the blood supply in the US. Next slide please.

Okay, so the rationale for this work. These filoviruses and HAV can be potentially transported by blood. Filoviruses are endemic in Africa and HAV is endemic United States. And then there have been few very well-publicized cases after Ebola virus brought to this country a few years back, but the potential of risk exists. There have been recording outbreaks of filoviruses, mostly Ebola virus, in Congo and some other parts of West Africa. And there has

been several episodes of upsurge, significant upsurge, in HAV cases in the United States, starting in 2006, which has spread to 37 Street. And then at the time this slide was made, there were like 44,000 cases, 27,000 hospitalizations, and 420 deaths at that time. FDA regulates flu viruses, and HIV products including vaccines, diagnostics, and blood donations. And Dr. Kaplan's research program is directed to fill these needs as needed and appropriate. Next slide please.

Okay, so, what are the research projects under these programs? So the research projects for filoviruses. I must say that these projects are being phased out now and will be discontinued in the near future. Dr. Kaplan's group has developed Filovirus BSL-2 neutralization tests that could be conducted at the bench rather than BSL-4. In collaborations, have developed an ultrasensitive Ebola virus antigen test. Participated to develop assays to determine Ebola virus sequence variation, an effort which was led by Dr. Robert Duncan, another PI in the lab. And then, performed analysis of anti-Ebola T-virus responses in animal studies.

Now coming to the HAV program, he continues his research on cell entry of HAV. He's exploring the prospect of hepatitis A cellular receptor 1 as a cell entry factor for hepatitis C virus is lower as a coreceptor. And then he has determined HIV infection by exosome. That was a major effort in the past four years. Next slide please.

So here's the result of the accomplishment, measured as publications, the four publications for viruses and four publications for HAV listed here. Next slide, please.

So these are some of the major findings, and this is focusing on his discovery of exosome mimicry model of HAV infection. And what he finds is that cargo delivery of exosomes requires two lipid receptors, HAVCR1 and NPC1, but not a viral envelope. Infectivity of exosomes from HAV-infected cells in mediated by cargo delivery of free viral RNA and not intracellular uncoating of viral particles. I get that's important finding.

And then, what are the implications of this? Now, Dr. Kaplan is exploring the ways how these exosome pathways can be targeted for novel therapeutic interventions to prevent viral infection, modulate exosome-mediated treatments, and then enhance mRNA vaccine delivery, if possible, by looking into this exosome mimicry pathway of HIV infection.

So where these works are heading now. So we are extending the knowledge on HAV cell entry projects to develop methods for pathogen reduction of non-enveloped viruses, because the current technologies of pathogen reduction don't work very well for non-envelope viruses. And then, analyze clinical markers of HAV infection in plasma from serial donations obtained during current HAV epidemics in in the United States. This is the work he's doing in collaboration with blood centers. Next slide please.

Okay, so I'd move on now to the research program of Dr. David McGivern on Diagnosis and Pathogenesis of Hepatitis Viruses that Threaten the Safety of Blood and Related Products. So these are the major goals and objectives: develop reference reagents to evaluate and standardizes nucleic acid assays; understand prevalence and impact of viral hepatitis in North America; develop novel models for studying hepatitis virus infectivity and pathogenesis. Next slide, please.

I think a little bit of introduction is in order here for those who are less familiar with this. So, there are different levels of panels that are developed here at CBER, and I guess globally. One of the international standards than they have are reference panels, different reagents, and then another nomenclature for secondary standards. And all of this depends on the rigor used in panel development and correct standardization and validation through collaborative studies. The main purpose of starting this program, Dr. McGivern, was to look into the risk of HEV and potential in blood supply in United States. And so to that end, he developed these HEV

secondary standards and nucleic acid standards, and he developed these heat-inactivated secondary standard for harmonization of Nucleic Acid Amplification Technology based assays for HEV detection. And then he took this panel and then calibrated again the standards against the WHO International Standard in a collaborative study involving 10 laboratories, and this study got recently published. So that was the one major purpose of starting this program, which has been accomplished.

And then, we just discussed about how we respond to the new threats. And with the coming of COVID-19 pandemic, you know, the risk became evident in early 2020, Dr. McGovern was called upon to develop this FDA reference panel for evaluation of molecular diagnostic devices for SARS-CoV-2. So this was the RNA panel, which was done on the behest of our sister Agency, CDRH, and was used at that time very extensively for evaluation of these UAs. And then, Dr. McGivern's lab participated in the Collaborative Study for the Establishment of the first WHO International Standard for SARS=CoV-2 RNA. So I guess these two he studies did occupy a major part of 2020 and 2021. And next slide, please.

Then, coming to his more basic studies, understanding the prevalence and disease impact of viral hepatitis in North America. For persons infected with hepatitis B virus and hepatitis C virus, disease outcomes are variable, but the underlying mechanisms are poorly characterized. The contribution of HEV to disease progression in persons with chronic liver disease is poorly understood. So, what is the research progress in these areas now? They characterized the prevalence and disease impact of acute HEV infection among persons living with chronic hepatitis B in the US and Canada. How acute HEV infection will worsen chronic hepatitis in individuals in North America? These studies published identified novel biomarkers. This was a major collaboration with the NIH, the liver's progression in viral hepatitis. And what came out of

this study was they showed that the gene, chitinase 3-like 1 gene, encodes a profibrogenic factor, which is overexpressed in the aging liver and in HBV- and HCV-associated cirrhosis. So this is a sort of non-specific marker for fibrosis, but I guess it explains the basis of fibrogenesis in the cirrhosis liver. And along the way they develop a novel sandwich ELISA for the detection of HEV-2 open reading frame 2 antigen in blood. So the implications are tremendous. It could be used for detection of acute detection of HEV infection and is being studied in animal models. Next slide, please.

So, coming to his studies and developing models for hepatitis virus infectivity and pathogenesis. So HEV transmission and pathogenesis are poorly characterized in part due to lack of small animal models of infection. And for HBV, the lack of robust cell culture models has limited investigation of virus-host cell interaction. Because generally the cell lines, those are used cell lines, established ones are poorly validated. So, Dr. McGivern's lab has conducted studies to develop novel and cell culture models for hepatitis virus infectivity for both HPV and HEV. And here are some of the results.

They establish a gerbil model of acute HEV infection in immunocompetent host for transmission pathogenesis studies. They establish a novel model of chronic HEV infection, which is probably more pertinent for blood safety perspective, which does not exist so far, using gerbils treated with the immunosuppressive drug tacrolimus. And then established HBV and HEV cell culture infection systems based on primary human hepatocytes, which are being derived from chimeric mice with humanized livers. This study was done in collaboration with an investigator in California. And next one, please.

Here is summary of accomplishments here in terms of publications, total of 10. So the HEV secondary standards, as mentioned, has been published now. - Host biomarkers of disease

progression in chronic HBV and HCV has been published. Prevalence and impact of acute HEV among persons with chronic hepatitis B has been accomplished. He has several research collaborative agreements with investigators at NIH and University of Southern California. Those are the ones who provide the liver sample cells in mice. And then the future directions include further deciphering the molecular events. Those happen in gerbil model during acute and chronic HEB infection.

One goal is to define the mechanism of cell injury and also to learn the global level, what happening in terms of immunity and while clearance. And then he will continue his studies. The cells culture systems that he has developed for HBC and HEV has enhanced the wire yield by several log folds. Now, that model will be not only used to study the widest post cell interactions, but also could be used to assess effectiveness of novel pathogen reduction technologies, which is becoming a major focus of the office level. Research against HPV and HEV using primary human hepatocytes because the viral loads are high enough now. So it'd be easier to measure the log reduction as the effect of pathogen reduction technology from chimeric mice with humanized livers. Next one please.

Moving on to the last investigator whose program is being presented today, Dr. Maria Rios, and her program Evaluating Pathogenesis and Markers of Arbovirus Infections and Developing Reference Reagents to Improve Blood Safety. Here are the major objectives there two major programs. First to reagents to evaluate and harmonize nucleic acid assays, and this has been a major focus of Dr. Rios' research for the past many years. And then they are conducting studies on pathogenesis and identification of biomarkers of flaviviruses using primary isolates from asymptomatic infections. The idea is twofold, to determine the impact of genetic variability

in flaviviruses infectivity in pathogenesis and then identification of biomarkers for differential detection of Dengue virus, West Nile virus, and Zika virus. Next one, please.

First, her research program on reference panel development for nucleic assays. So the projects, those have been accomplished already, and is the sum of research of many, many years. Reference reagents for arboviruses and for blood group genotyping were produced and validated through different means, and I'll go to a little bit more detail, and are now available for stakeholders for use. Some of these are routinely used a lot. This panel was used in the assay development and for licensure of assays. So, RNA references reagents and international standards for emerging viruses. For West Nile Virus, it has been RNA reference region available and been used for many years. Dengue viruses, all four genotypes. International reference reagent, Chijungunya became international standard, and Zika virus became reference reagent, which was very handy in a licensure of assays for Zika. In addition, DNA Reference Reagents for Blood Group Genotyping. 18 members covering 42 blood group alleles were developed. And this has been endorsed as WHO International Reference Agents for Blood Group genotyping. So at the phase it seems like these programs are in, these panels are sort of complete now on their own, but they will need to be continued to be refreshed as needed. Next one, please.

Coming to the second project, the first portion of it. We're studying Dengue virus, West Nile virus, and Zika virus using primary isolates and the impact of genetic variation in flavivirus infectivity and pathogenesis. The bottom line is most of these studies so far to look at the effect of genetic variability and infectivity in pathogen in separating virus strains are done with a laboratory adopted isolate. Which may not represent the true nature of viral genetics in terms of the current isolates. So therefore, what Dr. Rios' group has done, they decided to use the primary

isolates coming from ASM blood donors and use those viral isolations to study even events during infection outcome through these genetics studies.

So what are the major findings? As these studies have been done to some level for all these three viruses, but what is being presented today is using Zika virus' model. Comparative ZIKV study using cell lines and monocyte derived macrophage cultures showed augmented viral isolation using macrophage despite presence of antibodies. The study also revealed variability in isolation and growth patterns among 42 samples tested.

So the sequencing has shown that 12 Zika virus isolates had two major clades exhibiting genetic variability compared to reported variability from clinical isolates from publications. So the variability ranges from 8 to 54 nucleotide mutations and 2 to 11 amino acino acid substitutions per isolate. In summary, indicating a role these generative variations maybe playing in infection outcome, how different infections are different in respect to the host genetics. So some of these studies will be continued in the future.

And then what they have done is they've produced a two stable full length Zika virus reporter virus strains. So one is the nano Luciferase and the second is GFP. These have been developed to study the impact of genetic variability of pathogen assist, both in cell culture models and in animal models. Next one, please.

So, the second project is identifying differential biomarkers for dengue virus, West Nile virus, and Zika virus infections for detection and diagnosis. The reality is all these three viruses are generally co-transmitted in the same area. Individuals living there have antibodies which are highly cross-reactive, so the antibody assays become less useful in speciation which virus is actually currently infecting the individual, resulting in poor proper treatment options and overall impacts to public health. So these assays are useful, they're highly specific, but viable period

may be low. The time of infection when the sampling was then while load maybe quite low at the time of sampling.

And also, these NAS have limited feasibility in terms of where the assay is been done and heights, to put it so forth. So, the idea is to have a, because in early days the infections, the symptoms are indistinguishable, could be asymptomatic or could be milder nature, which later on progress into more severe disease. So early diagnosis is important in terms of better case management and a better clinical outcome. The one part of the study, which is complete now, they look at the immune biomarkers, soluble biomarkers. They look at total of 45 immune biomarkers, which patient cytokines, chemokines, and growth factors for discriminatory detection of retinal virus and virus were analyzed and found to be up regulated in asymptomatic infections and as compared to noninfected individuals. Out of those 45 we studied for Dengue infected individuals, 25 were upregulated; for West Nile virus, 5 were upregulated out of 45; and for Zika virus, 7 out of 45 were upregulated. So when you look at them cumulatively. looking for the features which are distinguishing between different viruses. TIM-1, IL-1ra, IL-4 and C3a factor were identified as potential biomarkers to differentiate between dengue virus, West Nile virus and Zika virus infections. This study is now published, and the idea at some point will be to expand the study into clinical samples.

And there's another major effort, ongoing study using micro-RNA as a biomarker for discrimination of dengue virus, West Nile virus, and Zika virus in asymptomatic individuals. And they have already found 21 up-regulations and 16 down-regulated mRNA compared to non-infected samples. So obviously this will need lot more work for these biomarkers to narrow them down further and see if they find an application in viral speciation or differentiation. So next slide please.

Okay, so looking at the accomplishments, publications. There was total of 17, and they are listed here categorized based on viruses and for genotyping for blood groups. Dr. Rios has many collaborations within NIH and also many in the field, also in Brazil and from blood establishments. She did secure outside funding, some intramural that is non-office funding.

And also the future directions include Zika virus reporter viruses. They will use this to investigate the impact of mutations on infectivity in cell cultures, replication, and pathogenesis, hopefully in animal models by using Luciferase, and to investigate the role of immunoglobin in pregnancy in collaboration with an investigator at Office of Cell and Gene Therapy. And then they will further investigate these upregulated soluble biomarkers of immune response as differential biomarkers in archive samples and in in vitro systems after infection in PMBCs and with each individual virus to see whether looking at these samples, PPMC is for infected individuals. They will see the upregulation in and production of the same markers. And then they will continue their research or miRNA as discriminatory tools for dengue virus and Zika virus using repository samples. I guess this was the last slide, so that's all I have, and I'll be happy to take questions.

Dr. Ziggy: Thank you so very much for reviewing the scientific accomplishments of lab, and I would like to open now the presentation to any questions from the Committee members. And please your hand and when call, turn on your camera and then your microphone prior to asking your question. I see a hand, yeah. Miss Cumming, Melissa?

Ms. Cumming: Yes. Good morning. Thank you so much Dr. Kumar. This was really an excellent presentation and a very impressive body of viral research. I had just one small question on slide four, you mentioned the plan to discontinue the filovirus program in Dr. Kaplan's lab, and it seems unfortunate, but I was wondering if you could maybe expand on that

decision and what that timeline looks like and if there are thoughts on. or any suggestions on. how that work might possibly continue. Thank you.

Dr. Kumar: So, the major challenge in resources, these things take major deductions. Kaplan was able to leverage these projects through NIH fundings, but the idea is, the projects are there, expertise there, if need is there. And also, we have to evaluate the direct list of blood safety also, in terms of… So those are the considerations, but the thought is not lost, also. The projects do exist. And if this need is felt at office, division level, Office level, Center level, I don't think it'll take us very long to come back to them. But the resources are the major challenge, actually. Becomes difficult for one principal investigator to focus multidisciplines. I hope I answered you satisfactorily.

Ms. Cumming: Thank you.

Dr. Kumar: But the resources are the lynchpin of everything we do. Yeah. As anywhere Yeah.

Dr. Ziggy: Thank you, Dr. Kumar, for the response. Any other questions from the Committee members? Seeing none. Thank you so very much. Thank you for the thorough evaluation. Well, and we're moving to the final presentation for today. I would like to introduce our next and final speaker in the part of the meeting is Dr. Indira Hewlett. She’s the Director of we at Chief of the Laboratory of Molecular Virology. And Dr. Hewlett, please turn your camera on and then unmute. The floor is yours.

Overview of LMV Research Programs

Dr. Hewlett: Thank you, Dr. Ziggy. And good morning, everyone. First of all, can you hear me? Okay. Thank you. so my name is Indira Hewlett and I'll be presenting an overview of the Lab of Molecular Virology, or the LMV, in the DETTD. Next slide.

So, the mission relevance of this program falls under the OBRR research priority that has the goal of assessing and promoting safety and effectiveness of transfusion transmitted infectious disease agent donor screening and supplemental tests. And most relevant to our group is retroviral diagnostics. And so the objectives that we work on are evaluating screening and confirmatory technologies for detection of these agents to enhance blood safety. We develop and evaluate reference panels for screening, particularly for retroviral diagnostics. And finally, we perform research on mechanisms of transmission and pathogenesis, focusing on retroviruses and TSE agents, which I'll talk about in a few seconds. Next slide, please.

The LMB has both a regulatory and research mission, as was mentioned by Dr. Nakhasi. We do both types of work. Our regulatory mission involves the review and approval of in vitro donor screening and diagnostic tests for HIV, HTLV, and retroviral agents. Recently this past year, we added bacterial detection assays to our portfolio, and we also engage in developing policies for Transmissible Spongiform Encephalopathies, or TSE.

Our staff also participate in developing review criteria and standards for approval of tests and policies related to their use in the intended setting. To support the review mission of the division and of our lab, and of course, the OBRR, the lab performs research on HIV and related retroviruses and co-infections in AIDS. We also characterize reagents for reference and later release panels for diagnostic and donor screening tests. You've heard about this from both Dr. Kumar and Dr. Nakhasi. And we are also performing research on bacterial detection and methods for removal and inactivation of bacteria in blood. And finally. there are studies on

pathogenesis of TSE agents, as well as validating detection assays, but some of these studies are winding down over the next couple of years. Next slide please.

So, to achieve our goals and objectives the lab is organized into two sections: the HIV and retrovirus section, which I head, and the bacteria and TSE section headed by Dr. Gregori. which was added to the LMB during this past year. The labs are staffed by staff scientists, contract fellows, and support staff who help us perform the research, and some of them are also engaged in review of applications. Next slide.

Next, I'll briefly describe some of the projects in each of these sections, starting with the HIV and retrovirus section which I had. In this group, we have three broad areas of study. The first one is the molecular diversity of HIV and its impact on diagnosis and pathogenesis. And in this area, we use molecular techniques to characterize HIV diversity and study the impact on diagnostics. We also develop diagnostic tools in the laboratory, as well as reference reagents for HIV assays. We also employ OMICS and other techniques to study pathogenesis to identify diagnostic and predictive biomarkers of various disease stages in HIV infection.

In the second area, we are investigating novel emerging diagnostic technologies and the bioinformatics that are needed for use of these technologies to detect and characterize viruses, particularly HIV.

Here we are focused more, more importantly, or more intensely, on NGS, or next generation, techniques and related techniques to characterize HIV variants, particularly drug resistant viruses in blood. And finally, during this past year we added and initiated some work on pathogen reduction in technologies for HIV and retrovirus. And this work is being done in collaboration with Dr. C from the office of Next slide. So I'll just briefly touch on and summarize each project in each of these project areas. In the next couple of slides. In terms of the molecular

diversity, we have genetically characterized a set of highly diverse HIV-1 viruses for the purpose of a reference panel and load-release panel development, which was discussed earlier in Dr. Nakhasi's talk.

As you know, HIV is genetically highly diverse due to mutation and recombination. And there, we have developed panels in the past, but there is an unmet need for HIB RNA and DNA reference reagents of predominant diverse HIV strains to evaluate viral load donor screening assays, and more importantly, the emerging latency assays for detection sensitivity of viral variants. Because the panels we've developed so far do not contain any of these diverse strains. They're focused more on the predominant strain that is circulating in the US. These FDA re reagents, when available, will provide a common set of standards to evaluate different diagnostic NAT assays and to compare them, especially when they're reviewed as Class II devices or what we call 510(k)s. For this work, highly diverse viruses from Cameroon and the US were cultured from PBMC and plasma, tested for viral load, and characterized genetically by Sanger and full genome sequencing. Next slide please.

So, the results showed that in our collection of specimens, we had multiple non-B subtypes and highly diverse recombinant mosaic forms that were identified using both Sanger and full genome NGS. These strains included major circulating recombinant forms and non-B subtypes that are circulating in the US – and this is an important point – and therefore, these viruses, when made into reference reagents or into panels in the future, will be relevant to the diagnostics that are used in this country. We also determine the viral load of stocks and assign values to each of the stocks for future use in formulation of large release and reference panels. Next slide please.

To summarize this work and the future directions, we have created a repository of highly diverse HIV viruses and plasma at SEPA that can be used as reference reagents for in the future for panel development. These viruses will be provided to the Office of Compliance and Biologics Quality for future panel development for donor tests as needed. And they will also be provided to the External Quality Assurance Program, an oversight laboratory, what we call the EQAPOL, of Duke University, which is a contractor of NIAID with whom we had an interagency agreement for this work, which uses reference reagents by diagnostic test manufacturer so they can evaluate the test for performance of these diverse trains. Currently, we are working on a highly diverse HIV DNA panel, and this would be for the purpose of latency assays. We are actually characterizing these reagents. We are not actually making the panel yet, but we are characterizing the reagents for latency assays to ensure patient and blood safety from HIV transmission by persons on PrEP, ART, and cure regimens. Next slide.

So in the next project, we embarked on developing an app, an HIV-1 drug resistance mutation app, for the purpose of using it to review sponsor NGS data. And the rationale for this work is that HIV drug resistance test developers use NGS platforms for product development. So there is a need for in-house bioinformatics tools to be developed and made available so that we can perform an FDA analysis of the sponsor data, rather than just accept what is provided to us. So one of our staff scientists developed an in-house graphical user interface computational tool, which is compatible with the FDA network to establish an independent method to analyze the data to support regulatory approval of the two applications that were submitted to the FDA. This app can also be used for review of future applications. Next slide.

So, what it involves is inputting the raw sequence reads into the app, running a program known as codefreq, and downloading this this file, and then running the center database, HIV

drug resistance database, against the data from the codefreq output file to come up with the assignment of drug-resistant mutations. The app was evaluated in house by testing a virus stock at various concentrations, 100, 1000, and 10,000 copies per mil and limited number of patient samples. And we found that this app could detect all the major drug resistant mutations and accessory mutations at the 5% level, which is what was claimed by the sponsor, at an HIV-1 viral load of 1,000 copies per mil. And this work has been completed, although we would like to test a few more samples, but future efforts are aimed at transferring the app to the CBER bioinformatics platform for internal use in the regulatory review of applications. Next slide.

In the next project we are focusing on disease stage specific host biomarkers of HIV infection. And the rationale for this work is that pre-exposure prophylaxis, or PrEP, and antiretroviral therapy, ART, regimens have been implemented nationwide in order to reduce and or eliminate HIV infection at various timelines that have been proposed. Which, of course, do getting pushed based on funding and strategy and so on.

But early treatment, which is now universally recommended, causes HIV markers to be undetectable in blood by current HIV diagnostic and donor screening assays and may therefore pose a concern for patient and blood safety. The goal of our work is to identify disease-stage specific, host biomarkers, for example, micro RNAs and long non-coding RNAs in addition to other host molecules and signaling pathways as surrogate markers of virally suppressed disease stages, and in patients on HIV cure regimens and strategies. Next slide.

The work involved performing the study in four different phases in the first phase what we call the biomarker discovery phase. A limited number of samples, specifically three samples from each category. The controls, RNA positive, antigen positive, and antigen antibody positive, were screened using PCR arrays to identify differentially expressed miRNAs. And potential

miRNAs were identified and selected for further investigation. And the second phase involved validation. And in the validation phase, these candidate miRNAs were further validated using quantitative PCR. And next, based on the validation, these miRNAs were grouped together using a multivariate analysis to develop a panel, a combination of miRNAs that could serve as potential biomarkers. And this, what we call the diagnostic panel, was further evaluated using a blinded set of samples. And this work has been published in EBioMedicine, but what we found was in the next slide, please.

We found a number of different miRNAs that could be grouped together to form a micro-RNA panel, that were able to detect HIV in a very early phase of infection, what we call the eclipse and the pre-eclipse phase, with a high degree of sensitivity and specificity. And this panel could accurately detect samples from patients in the early stage with undetectable plasma HIV RNA markers. That's both RNA and HIV-1 p24. So, our future studies are aimed at validating the RNAs with additional patient samples and being reached out to collaborators to obtain samples that would be from patients on cure regimens, or patients who are virally suppressed to look at the ability of these mRNAs to identify those patients and perform according to the stage of infection of these of the patient. We would like to develop a diagnostic miRNA panel to identify HIV-1 infection in latently infected or ART patients with undetectable viral markers, and to identify and validate other small RNAs, including non-coding RNAs and transfer RNAs for various HIV disease stages. And this work is already ongoing, and we have some preliminary results from these studies as well. Next slide. They look promising.

Finally, I'll just briefly summarize a study on pathogen reduction technologies where we used 405 nanometer visible blue light to look at the inactivation of HIV-1 in plasma. And this work was done in collaboration with Dr. C.D. Atreya from the Office of Blood. The rationale is

that current PRTs are known to have adverse effects on coagulation factors of plasma and platelet functions. 405 nanometer blue light was studied as a potential alternative to existing PRT, as it is lethal at all levels to microorganism, but it does not seem to have adverse effects on the host cell. Next slide.

To summarize this work, five individual plasma samples were treated with this light and for varying lengths of time. And we found that samples treated for five hours showed a significant reduction in infectivity of HIV-1 compared to controls or samples treated with a shorter period, for example, 30 minutes. So, our conclusion is that 405 nanometer light inactivated HIV-1 effectively in plasma, and the future work is aimed at studying the mechanism of inactivation and evaluating other PRT for effects on HIV-1infectivity. And at some point, also look at it in, in the context of platelets and whole blood. Next slide.

That summarizes the key examples of some of the work that is going on in the HIV section. Next, I'll summarize some of the work in the bacterial and TSE section, which is headed by Dr. Louisa. this group has, as its research goals to develop a blood assay to detect transmissible spongiform encephalopathy, TSE, agents, and to maintain safety of therapeutic products, including blood. And the second focus is to develop novel methods of bacterial reduction and detection in blood and blood components to improve the safety of blood transfusion from bacterial transmission. Next slide.

The rationale for the TSE research is that TSEs, or prion diseases, are incurable neurodegenerative diseases that have occasionally been transmitted to recipients of therapeutic products. There's a theoretical risk that exists of sporadic Creutzfeldt-Jakob disease, that is, sCJD, transmission from human cellular and tissue-derived products used in regenerative medicine. So there is a need for a rapid, sensitive, and specific sCJD blood test, and there's an

unmet need for relevant reagents to develop and validate these blood tests. So, the group addressed this unmet need by producing blood from macaques infected with variant CJD as a surrogate for human sCJD blood. Next slide, please.

The results are that they generated vCJD-infected macaque blood as reagent for assay development, the use of blood to detect abnormal prion proteins, that is, PrP-TSE, and other biomarkers that might be suitable for preclinical sCJD diagnostics. So, PrP-TSE and a host biomarker neurofilament light chain are in macaque blood months before clinical onset. And these macaque blood materials are now available as reagents to develop and validate blood tests for either PrP-TSE or non-PrP-TSE. The future work is focused on completing the project on detection of PrP-TSE in preclinical macaque blood and evaluating sCJD and familial CJD blood samples using these markers. Next slide.

So the second project they're working on, in this program area that this group is working on is bacterial research. And the rationale for this program, particularly on pathogen reduction, is that methods of pathogen reduction are available for plasma and platelets, but not for red blood cell concentrates and whole blood. There's a research gap that requires developing novel pathogen reduction methods for all blood components. And we know this quite well. So, the group addressed this research with a new project focused on capture of bacteria spiked in platelets and whole blood using affinity ligands. Next slide.

So, they basically selected nylon filaments as the solid support of the ligands. They produced a panel of nylon materials containing different functional groups – it could be charged, polar, or hydrophobic – to test as binders of bacteria. And they've screened these dyed nylons with *E. coli* and *S. epidermidis* and identified the best binders of these materials. The future work will be focused on bacteria spiked in platelets and whole blood, the detection of bacteria that is

concentrated on the dyed nylon, and to investigate the quality of platelets and whole blood after they've undergone treatment using these filaments. Next slide.

That concludes the presentation of the work in each of the sections in the LMV.And I will close by acknowledging the people in my own who contributed to the, the work I presented. And the next slide. As well as acknowledgements from Dr. Gregori's lab, with her staff members and the various collaborators and support from both FDA and DETTD. Thank you. I'm happy to take any questions.

Q & A

Dr. Ziggy: Thank you, Dr. Hewlett for this extreme well-organized and thorough presentation. I would like to open the discussion of the presentation. I see Dr. Basavaraju. Yes. Can you…?

Dr. Basavaraju: Hi. Thank you. I had a quick question about — I guess two questions. One is the, the last set of slides that you showed on the pathogen reduction studies, and you proposed spiking whole blood with bacteria and then spiking platelets with bacteria. But my understanding of pathogen reduction technology was that the advantages in red blood cells would not be to reduce the risk of bacterial contamination, but rather for the other pathogens, viruses, and parasites. So I was wondering why you chose a study design to look at bacteria in whole blood.

Dr. Hewlett: Well, I think – sorry.

Dr. Basavaraju: Yeah. Is it because you are assuming that if you applied the pathogen reduction step at the whole blood process to the derived components, like platelets, would also be presumably path introduced? Yes, yes.

Dr. Hewlett: Yes, yes. I mean, that's the challenge, I think, that is before us. There's a lot of work that's been done with the other compartments. So the whole blood area, I think, appears to be the one that needs more focus and more attention. So that is, initially it'll be the — you're talking about the nylons, right? So, the nylons would be evaluated with all matrices, because they haven't been tested with any of the matrices. So it would be all of them. But the challenge in blood safety is, of course, whole blood. Because whole blood is, of course, as you said, you know, converted into — it's not just whole blood, it's red cell concentrates, because that is actually what is used today. But there's a lot of interest in looking at whole blood as a potential product that could be used in emergency situations or in other scenarios. So that's something that is still on the table as a component that one should be looking at to see if it's feasible. The feasibility is a different story, right, but it's something that is a challenge. And it's something worth looking at. So that is still on the table. Dr. Gregori would like to start with the simpler matrices and then move towards that. So that's the plan.

Dr. Basavaraju: The other question I had maybe is more, I guess, asking you to speculate. We have, every few years, a new pathogen that's identified as transfusion transmissible. And for decades now, the standard has been to do NAT or serology or something on blood donations. But how far do you think we are from moving into more advanced molecular detection methods for screening blood donations? So you could get away from NAT tests that are multiplex or identifying one pathogen or something, and get more towards

identifying whether a blood product has multiple other potential transfusion transmissible agents?

Dr. Hewlett: Yeah, that's a very good question, and thank you for that. Our entire division is interested in that approach of being able to be able to look at multiple things in different groups of pathogens, either using technologies like NGS or, you know, other -omics technologies, where you could spot different things and the representative sequences of different groups of pathogens, and so on. That's where we'd like to go. But it has its challenges. You know, it's not easy to screen for everything and not be aware. There are issues, of course, donor notification, deferral, and so on. There's that whole side of policy in implementing those types of assays. That needs a lot of discussion and it's been discussed previously in one or two workshops that we've had.

But the issue really is how much information do we want to have? You know, we know that people like Charlie Chew, you know, they've got arrays that can pick up every class of viruses, and you can put parasites and bacteria on it as well. And then you've got the NGS methodology where you can do agnostic NGS and find a whole slew of things in a blood sample. We have a program in our lab actually Dr. Ragupathy, is one of the main players in this program, is trying to develop different ways to do agnostic sequencing to see what we would find in blood donors or in — of course, febrile illness is the main target. That's where people are looking for new pathogens. But if you just want to look for pathogens in a blood donor, if you took an agnostic NGS methodology and ran it and then, you know, try to decipher what is in the blood, what happens is you get a whole bunch of things and you've got to sort through it and you've got to find ones that are meaningful.

So there's a lot of issues with the methodology, but it's certainly the one that I think will be coming forward in the future. Maybe not in, in the very near future, but that's the thinking. And it seems to be on the horizon, but it's not quite here yet. Thank you for the question.

Dr. Basavaraju: Yeah, thank you.

Dr. Ziggy: Thank you so much for the question and presentation. Thank you. I would like to thank at this point all five presenters for very, very good, great presentations and very informative presentations. And I'd like to call this Committee for break. We'll be back at 11:35 Eastern time. So now you have 12 minutes or so for yourself. Thank you so much.

Open Public Hearing

Dr. Ziggy: Great. So welcome back from the break, thank you again for joining us. This is the part of the meeting where we have an Open Public Hearing and I will read a formal statement, Open Public Hearing announcement for the particular matter of general applicability meeting, or PMGA. Welcome to the open public hearing session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that is important to understand the context of an individual's presentation. For this reason, FDA encourages you, Open Public Hearing speaker, at the beginning of your oral statement to advise the Committee of any financial interests relevant to this meeting. That is, a financial relationship with any company or group that may be affected by the topic of this 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 the issue of financial relationship at the beginning of your statement, it'll not preclude you from speaking. After reading this statement, I would like to now hand off the presentation, this portion, giving to Christina Vert.

Ms. Vert: Thank you, Dr. Ziggy. Before I begin calling the registered speakers, I would like to add the following guidance. FDA encourages participation from all public stakeholders in its decision-making processes. Every Advisory Committee meeting includes an Open Public Hearing session, during which interested persons may present relevant information or view. Participants during the OPH session are not FDA employees or members of this Advisory Committee. FDA recognizes that the speakers may present a range of viewpoints. The statements made during this open public hearing session reflect the viewpoints of the individual speakers or their organizations and are not meant to indicate Agency agreement with statements made.

With that guidance, I would like to begin to introduce our first speaker. If you could please pull up her presentation, Dr. Misztela.

Dr. Misztela: Good morning. I hope you can hear me, so I think we can proceed to that next slide. Good morning, ladies and gentlemen, my name is Dominika Misztela. I'm the Head of Global Regulatory Policy at the Plasma Protein Therapeutics Association, and today I will present you a brief overview on behalf of the PPTA and our member companies. Next slide please.

The PPTA, we are an industry organization representing the collectors of source plasma, as well as the manufacturers of plasma derived and recombinant therapies. We provide more than 60% of the world's need for source plasma used to manufacture plasma protein therapies, and we also supply close to 80% of the world's safe and effective therapies. Here is a little

overview of our membership, our collectors. We predominantly collect in North America. The majority of our collection centers is in the United States, with a few centers recently opened in Canada, and we also collect in four countries of the European Union. Our industry is global. Therefore, any changes to regulations, to provisions for our industry, have to be seen in a global context. And we are extremely appreciative of the FDA's efforts to engage with international stakeholders around the globe to promote their policies on donor health, donor selection, and collection practices for source plasma. Next slide.

This is a small overview over how we have been impacted by COVID-19 in North America. As you see here, over the last two years, we have had approximately a 20% decrease in our collections due to Covid, whilst at the same time the number of collection centers are increasing. So this has been quite impactful for our industry. And as plasma protein therapies take between 7 and 12 months to be manufactured, the knock-on effect on availability of these therapies can only be seen later. Our 2020 data will be released sometime in January. Next slide please.

We are extremely grateful to the US FDA specifically CBER, through helping us by mitigating COVID-19 impacts. The US FDA has released a range of alternative guidances in 2020 that have allowed us to apply extended donor selection criteria to be able to have more donors in our centers, as well as to release more plasma for manufacturing. Additional guidances have been issued in 2020, and we are working with the FDA too, and we're hoping to have them finalized soon. These relate to blood pressure and eligibility requirements, as well as a range of compliance policies. Also, the FDA has been extremely helpful in making sure that our centers are compliant and stay compliant throughout the pandemic, through hybrid and remote inspections. Next slide, please.

We have also engaged in, in a range of collaborative efforts, both on state and federal level. On the federal level, we have partnered with the Department of Health and Human Services to engage in an awareness campaign, a 'Giving equals Living'. This is supported by the members of Congress, and it aims to mitigate the impacts of COVID-19 for both blood and plasma collections by supporting this campaign. We have also set up a plasma caucus, which fosters educational efforts in Congress, first of all, during the COVID-19 pandemic, and we are continuing those educational efforts throughout in Congress. Next slide, please.

We are also extremely active on social media by promoting the need for increased plasma collections, the safety of plasma donation, as well as the high standards and our own standards programs for our donors, our centers, and also our products. You can follow us on LinkedIn and Twitter. We also are extremely active on other media channels. Next slide, please.

As we are moving to the new normal of the COVID-19 pandemic, we welcome the collaboration that we have established with the US FDA, specifically CBER, on a continuous basis to address, for instance, emerging infectious diseases. We have our own expert committee, the so-called Global Pathogen Safety Working Group, which assesses emerging infectious diseases and impact on the safety of our therapies. It has been conducted for COVID-,19 and most recently for monkey pox. We are looking forward to collaborating on how we transition away from the public health emergency and alternative guidances issued by the US FDA. We are looking forward to see how the US FDA will implement the outcomes of the ADVANCE study, which recently has completed recruitment. Certainly, we're looking forward to working with the FDA when it releases the guidance for blood pressure pulse in donation suitability. And we are looking forward to continuing our discussions with CBER on total protein testing and syphilis testing for source plasma donors. And I believe with this, my time is over. Next slide please.

So, I would like to thank the Blood Product Advisory Committee for the opportunity to present on behalf of our membership. If you have any comments, any questions, you're most welcome to contact me at my email addresses below. Thank you very much.

Ms. Vert: Thank you, Dr. Misztela. And call on the next Open Public Hearing speaker, and I'll just wait for the slide. Mr. Williams, please go ahead, make your statement.

Mr. Williams: Hey, both myself and my organization have no financial interest or relationships affected by these statements. We understand that the Committee was not intending to hear about the MSM blood donation deferment policy today, and because of that, we thank you for the opportunity to share our public comment.

Since the 1980s and since 1977 with the retroactive deferral policy at implementation, queer men have been turned away from donating blood. The lack of scientific information of HIV and AIDS due to its novelty. The blanket deferment was the most informed decision that the Committee could have taken with the limited information that you had during the crisis.

With the scientific advancements, research and breakthroughs in the realm of HIV and AIDS, the blanket deferment is no longer necessary, nor is it supported by science. The implementation of nucleic acid testing allows for HIV to be detected in a donation conservatively between 10 to 33 days but has research supporting its ability to detect HIV as early as three days after a patient is infected. Both of these are significantly lost in the current three-month deferral period. The CDC states that the risk of HIV transmission through blood donation after nucleic acid testing is one in 1.5 million, a significantly low risk.

Furthermore, every donation is tested, and every donor has the potential to carry HIV, not just queer men. The current deferment policy turns away a queer man who is in a monogamous relationship, who is tested for STDs regularly and only has safe sex. At the same time, a

heterosexual donor can have as many sexual partners as they wish, be unaware of their STD status, and never practice safe sex, but they will still be permitted to donate. The policy is ineffective as stopping high risk donors while simultaneously preventing low risk donors from giving blood. Screening prior to donation should focus on high-risk activities, not a donor's sexuality. High risk activities can be changed, sexuality cannot.

Earlier this year, the Red Cross declared that we were in a blood crisis, the worst shortage in over a decade. This shortage of donation has not ended, and the blood supplies across the country are down to less than a day a supply in some instances. We do not need to stress to you that there is no alternative for human blood donations. We have seen the Committee's openness to adapting previous recommendations for deferral with this year's revisions to blood pressure guidelines and the former geographical restrictions for Creutzfeldt-Jacob Disease. With the shortage, blood centers cannot afford to turn away healthy donors.

The United States and the Food and Drug Administration prides itself on being a global leader in various industries. We train world-class physicians. We develop lifesaving drugs. But on the MSM blood donation, we are not at the top of the class. Other countries have updated their MSM deferment policies over the past few years. Canada implemented a new policy just four days ago and removed all questions related to sexual orientation. France ended their deferment policy for queer men in March of this year. Greece also removed their screening questions on sexual orientation this year. Last year, the United Kingdom moved away to allow queer men who are in monogamous relationships for three months to donate, citing it as discriminatory. Ireland has plans to institute an individual risk assessment this year. Lithuania asked all donors the same questions, none of which cover sexuality. Not all of these policies are the same, but all of them are less discriminatory than this country's three-month deferral policy.

The advanced study has been assessing the safety of a transition to an individual risk assessment. We hope that the Committee will review these findings of the study and work to implement an updated deferral policy soon. This policy has turned away queer men from donating blood for over three decades. This policy is discriminatory. It is wrong, and it holds queer men to a higher standard than their heterosexual peers. The policy is not effective at preventing all high-risk donors, and it goes too far by deferring low-risk donors.

Additionally, with advances in the screening of donations, the risk of HIV transmission is incredibly low. Blood centers do not need to turn away queer men, and with the current blood shortage, they cannot afford to. I would like to donate blood. If I was permitted, I know that I would give blood as soon as I was eligible every few months, and I know that I'm not alone in this.

If not in the interest of queer men who are being discriminated against, consider the patients who are having procedures delayed, the blood centers who are unable to meet the demands of their communities, and the medical facilities that are limited in caring for patients. If there's a more effective way to advocate for this change, please let us know. We would like to utilize both your time and our own in the most effective way possible. Thank you.

Ms. Vert: Thank you, Mr. Williams. And this concludes the Open Public Hearing session for today. And now I will hand over the meaning back to our chair.

Dr. Ziggy: Thank you very much to our participants in the Open Public Hearing. Now, I'd like to end our Open Session, and at this time, I would like to request all Panel members and FDA leadership to stay connected. Thank you for all who made presentations.

Break for Closed Session

Meeting Adjourned After Closed Session