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

118th Meeting of the

Blood Products Advisory Committee

June 22, 2018

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

TABLE OF CONTENTS

PROCEEDINGS (11:10 a.m.)

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

MR. EMERY: Good morning. I am Bryan Emery. I am the designated federal official for today's 118th meeting of the Blood Products Advisory Committee. I am about to read the conflict of interest statement, and actually, we'll first do a roll call, and we'll have an introduction of everyone.

Dr. Priola, are you on the line?

DR. PRIOLA: Yes. I would like to also welcome everybody to the 118th meeting of the Blood Products Advisory Committee. I am going to be the acting chair today, for both topics, which are reports of site visits for intramural research programs in both the Division of Plasma Protein Therapeutics and the Division of Emerging and Transfusion Transmitted Diseases.

So, I think I'd like to ask everybody to go around the table first, and then on the phone, to give their name and affiliation and the research work that they do. If we could start with the people currently in the room, I think Dr. Wilson, start with you?

DR. WILSON: Hi, good morning, Dr. Priola and the committee. This is Carolyn Wilson, associate director for research at the Center for Biologics.

DR. ATREYA: This C.D. Atreya, associate director for research, Office of Research and Review.

DR. NAKHASI: Hira Nakhasi, acting deputy office director for the Office of Blood Research and Review.

DR. HOBSON: Peyton Hobson, deputy division director, DETTD.

DR. ASHER: David Asher, laboratory chief, Laboratory of Bacterial and Transmissible Spongiform Encephalopathy Agents, Division of Emerging and Transfusion Transmitted Diseases in the Office of Blood Research and Review, and here today I'm representing not only myself, but Luisa Gregori, who could not be here today. She's a principal investigator under review, as am I.

DR. HEWLETT: This is Indira Hewlett. I am chief of the Lab of Molecular Virology in the Division of Emerging and Transfusion Transmitted Diseases in the Office of Blood.

DR. KAPLAN: This is Gerardo Kaplan. I am a principal investigator at the Laboratory of Emerging Pathogens at the DETTD.

DR. PRIOLA: Thank you, and on the phone, Bryan, I don't have a complete list of who is on the phone. Could you call people off so they can introduce themselves?

MR. EMERY: I will do that, thank you. It'll be a part of introductions. The first person I have on my list is Dr. Suzette Priola.

DR. PRIOLA: This is Sue Priola. I'm a prion researcher at the Rocky Mountain Laboratories in Hamilton, Montana, and that's an off-campus branch of NIH.

MR. EMERY: Next on my list is Dr. Judith Baker.

DR. BAKER: Hi. Director of Public Health for the Center for Inherited Blood Disorders in Orange, California, and adjunct assistant professor at the Division of Pediatric Hematology/Oncology at the University of California, Los Angeles.

MR. EMERY: Excellent, thank you. Dr. Alfred DeMaria.

DR. DEMARIA: Hi, I'm medical director of the Bureau of Infectious Disease and Laboratory Science at the Massachusetts Department of Public Health, and the state epidemiologist.

MR. EMERY: Welcome. Dr. DeVan?

Dr. Chitlur?

DR. CHITLUR: Hi, this is Meera Chitlur, from Children's Hospital of Michigan in Detroit. I'm the director of the Hemophilia Treatment Center, and also the special coagulation laboratory at Wayne State University and Children's Hospital of Michigan. Thank you.

MR. EMERY: Dr. Richard Kaufman.

Dr. Andrei Kindzelski.

Dr. Susan Leitman.

DR. LEITMAN: Hi, this is Susan Leitman, director of the Medical Research Scholars Program, formerly deputy chief of Transfusion Medicine, at the National Institutes of Health in Bethesda, Maryland.

MR. EMERY: Dr. Roger Lewis.

DR. LEWIS: Hi, this is Roger Lewis, I'm the chair of emergency medicine at Harbor-UCLA Medical Center, in Torrance, California, and my expertise is in clinical trial design and data analysis.

MR. EMERY: Dr. Robert Rees.

MR. REES: Good morning, this is Robert Rees. I'm the manager of the Blood Bank Licensing and Regulatory Compliance Program for the state of New Jersey, within the Department of Health.

MR. EMERY: Dr. Martin Schreiber.

Dr. Amy Shapiro.

Dr. Jack Stapleton.

DR. STAPLETON: Hi, this is Jack Stapleton. I'm an infectious disease physician and professor of internal medicine and microbiology at the University of Iowa. My research areas are positive strand RNA virus biology, and vaccine trials, and my clinical interests are HIV.

MR. EMERY: Dr. Susan Stramer.

DR. STRAMER: Good morning. This is Susan Stramer. I'm vice president of scientific affairs at the American Red Cross. I'm the industry representative to the committee, and I'm also chair of the AABB's transfusion transmitted diseases committee.

MR. EMERY: Thank you all. I'll quickly go back over the people that didn't answer, in case you've now been able to get on.

Dr. Michael DeVan.

Dr. Richard Kaufman.

Dr. Andrei Kindzelski. Dr. Martin Schreiber.

DR. SCHREIBER: Hi, this is Martin Schreiber, I just got the access code. I'm chief of the division of trauma, critical care, and acute care surgery at OHSU. I'm a trauma surgeon, and my research areas are novel blood products.

MR. EMERY: Dr. Amy Shapiro.

DR. SHAPIRO: Hi, I just got the access code. I'm a pediatric hematologist, medical director and CEO of the Indiana Hemophilia and Thrombosis Center in Indianapolis, and my research interests are clinical outcomes of patients with rare coagulation disorders and hematologic disorders, as well as new therapeutic agents.

MR. EMERY: Thank you. Welcome, everyone. There's someone else has come into the room. I'll let her introduce herself.

DR. VERDUN: Hi, I'm Nicole Verdun, the acting office director for the Office of Blood Research and Review.

MR. EMERY: Thank you. I'll read some regular notes for everyone, and then I'll go into the conflict of interest disclosure statement.

Agenda Item: Conflict of Interest Statement

MR. EMERY: Once again, good morning. I am Bryan Emery, the designated federal official for today's 118th meeting of the Blood Products Advisory Committee.

Ms. Joanne Lipkind is the committee management specialist, and she can assist you with any needs at the tables located in the hall. I'd like to welcome all of you again to the 118th meeting of the Blood Products Advisory Committee held in the FDA White Oak Great Room.

Dr. Suzette Priola is the acting Blood Products Advisory Committee chair for today. The CBER press media contact is Ms. Megan McSeveney, who may be in the audience later in the morning, and Dr. Chanda Chhay is the transcriptionist. I'd like to request that everyone please check your cell phones and pagers to make sure they are turned off or in the silent mode. Please also remember to

speak directly into the microphones at all times and please identify yourself; it is helpful to the public, people tending by webcast, and the transcriber.

For those members on the phone, please remember to place them on mute while you are listening in order to decrease any background noise. For those around the table in the audience, coffee, drinks, and snacks are out the doors and to the right, located at the kiosk. There are restrooms out the doors and to the right at the end of the hall. All committee topic discussion needs to be done in a public forum and not in groups during breaks.

The FDA and public needs your advice, thoughts, and expertise. The public and industry must stay behind the stanchions and in the audience area. Please do not enter into the FDA or BPAC committee table area. Please wait until the open public hearing designated time to make any remarks using the center aisle microphone.

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

The Food and Drug Administration is convening today's meeting of the Blood Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all participants of the committee are special government employees, SGEs, or regular federal

employees from other agencies that are subject to the federal conflict of interest laws and regulations.

The following information on the status of this advisory committee's compliance with federal conflict of interest laws including but not limited to 18 U.S. Code Section 208 of the Federal Food, Drug, and Cosmetic Act is being provided to participants at this meeting and to the public. FDA has determined that members of this advisory committee are in compliance with federal ethics and conflict of interest laws.

Topics 1 and 2 listed below are determined to be a non-particular matter and there are no affected firms identified for this topic and no prescreening of the members and consultants was conducted. Based on this agenda topics, it has been determined that the overview presentations on the research programs do not pose actual or an appearance of conflicts of interest, with regards to the agenda.

In the morning open session, under topic I, the committee will hear presentations on the research programs in the Laboratory of Emerging Pathogens, Laboratory of Bacterial and TSE agents, and from the Laboratory for Molecular Virology, in the division of Emerging Transfusion Transmitted diseases, Office of Blood Research and Review, Center for Biologics Evaluation and Research, FDA.

After the conclusion of the open session the meeting will be closed to permit discussion where disclosure would constitute an unwarranted invasion of personal privacy in occurrence with 5 USC 552b(6). In the afternoon, in open session under topic II, the committee will hear presentations on the research program in the hemostasis branch in the Division of Plasma Protein Therapeutics, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA.

After the open session, the meeting will be closed to the public to permit discussion where disclosure would constitute an unwarranted invasion of personal privacy in occurrence with 5 USC 552. Dr. Susan Stramer is serving as the industry representative. She is employed by the American Red Cross. It is to be noted that the industry representatives are not special government employees, and are nonvoting members of the committee; hence, they do not participate in the closed sessions and do not have voting privileges.

Dr. Baker is serving as the consumer representative for this committee. Consumer representatives are appointed special government employees and are the voting members of the committee. Hence, they do participate in the closed sessions and do have voting

privileges. The conflict of interest statement will be available for review at the registration table.

We would like to remind members, consultants, and participants that if discussions involve and products or firms not on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude themselves from such involvement and exclusion will be noted for the record. FDA encourages all the participants to advise the committee of any financial relationships that you may have with firms that could be affected by the committee's discussions.

That ends the reading of the conflict of interest statement. Dr. Priola, I turn the meeting over to you for further comments.

DR. PRIOLA: Okay, thank you, Bryan.

I think we'll just go ahead and get started with the presentations in the open session, so the first presentation is Dr. Carolyn Wilson, who is the associate director of research for CBER.

Topic I: Review of the Research Programs in the Laboratories of Emerging Pathogens, Bacterial and Transmissible Spongiform Encephalopathy Agents, and Molecular Virology, Division of Emerging Transfusion-Transmitted Diseases (DETTD), Office of Blood Research and

Review (OBRR), Center for Biologics Evaluation and Research (CBER)

Agenda Item: Overview of CBER Research Programs

DR. WILSON: Thank you. I'm going to try to just orient you briefly to the center and the research program and why we do research here, and the site visit process.

I want to start by thanking Drs. Priola and Stapleton for serving as co-chairs of this particular review of the group and to also put the entire AC on notice that we do periodically ask for volunteers to serve as chairs and co-chairs of these site visits, and it's a really important responsibility in order to provide an objective external review of the research programs to continue to make sure they're of high quality.

So I know this group obviously realizes we regulate blood and blood products and blood components. We also in our center regulate a variety of other products including cell and gene therapy, certain tissues, xenotransplantation products, certain devices, vaccines, therapeutic probiotics, and allergenic products.

We see the role of research as advancing product development and supporting our regulatory mission, and this graphic helps to represent what that really means to us, and we see everything starting with a public health issue

that may drive the development of a novel product, but oftentimes new products may pose regulatory challenges.

Maybe we don't have enough of an understanding of the mechanism of action to help advise how to develop a potency assay, perhaps there's not a good animal model, maybe reference materials need to be developed, and so on. And so that's where regulatory science, a term you've probably heard over the years, through a combination of both discovery research and targeted development of new tools can help to address the scientific gaps and inform our regulatory policy and decision-making.

As we get better guidance out to sponsors, that helps to improve the data that we receive and make those benefit/risk decisions so that at the end of the day we hope, like you, that we can license a product that will be both safe and effective to address that public health issue. And of course, it doesn't stop there, because the post-market surveillance is an incredibly important part of our mission as well.

So we view our regulation of biologics as being collaborative, where research is one of several elements that we use to evaluate the biologics that we have regulatory responsibility for, and it's important to note that our research scientists are what are called researcher reviewers. What this means is that not only are they

active scientists in their field, going out to scientific and professional meetings to hear the science that's of the day, and that hasn't yet come to our doors, but they're also actively involved in the review process as well, reviewing submissions, going out on inspections, participating in development of guidance and policy documents, advisory committees, workshops, and so on so that they also are at the front lines, seeing what's coming in to the FDA, and can use their expertise to identify where the gaps are, and that way we can really make sure we're addressing the most important science to support development of these innovative products.

So again, we view the benefits of our research program as preparing for future innovative products, as well as public health challenges. We develop tools and data that are available to all stakeholders since we publish our results in the peer reviewed literature, and that by doing so we support development of product classes as opposed to any specific one product. We recruit and maintain highly trained scientists so that we also have the necessary expertise to review those regulatory submissions and that the research program is helping to fill gaps to inform policy development and regulatory decision-making.

In the center we have an array of scientific expertise, including some specific technologies that are

used in evaluation of the products that we regulate. We are exploring how these technologies can be better applied to evaluation of the products we regulate. As you would imagine we have a lot of microbiology and immunology expertise, biochemistry, molecular biology, cell developmental biology, and a relatively new program in tissue engineering and microphysiologic systems.

As you would imagine, we're also very rich in epidemiology, biostatistics, and another relatively new but growing area of bioinformatics. Our lab facility has core facilities to support our research programs in several major areas including flow cytometry, confocal and electron microscopy, biotechnology which includes high throughput sequencing or next gen sequencing using Illumina HiSeq and MiSeq, and we also have developed a bioinformatics support for NGS data analysis and storage.

We also have a state of the art vivarium to support any animal research including an imaging facility that has MRI, digital x-ray, IVIS, and ultrasound NCT, and we have procedure rooms for both BSL2 and BSL3 requirements as well as a transgenic derivation facility.

One of the areas that prior advisory committees have commented on is whether or not we do appropriate mentoring of some of our younger principal investigators. In order to address that, because we're a relatively small

center with about 80 principal investigators working in a variety of different areas, we've developed over the last couple of years the CBER peer mentoring group, which is a monthly meeting. It's an informal peer mentoring group. We always have one senior PI who has agreed to oversee the discussion, but it's really open to everybody, all the principal investigators to bring up issues about how to manage their laboratories in a variety of different topics that have been of use to them. We've gotten a lot of really good feedback from the peer mentoring group about its utility, and they also have served as a great sounding board for developing solutions to some problems that they've identified through these discussion groups.

So obviously we can't do everything on our own. We have a very broad regulatory remit, and so we actively collaborate with the external community. This is a map from our FY17 Research Reporting Database just showing that we collaborate throughout the United States, we collaborate internationally, and we collaborate with a variety of different sectors. We have many collaborations with academia, obviously other CBER and non-CBER colleagues within FDA, other government agencies, international as well as industry and nonprofit.

So our research management processes. We have in recent years stood up a regulatory science council which

provides some governance and helps to advise the center director in developing regulatory science and research goals, as well as office-specific goals and objectives, and you'll hear more about those in subsequent talks. We've developed a research impact framework, and we also have processes for external peer review which the site visit represents, but also internal peer review as well.

So the four research goals that the RSC has endorsed are to advance the scientific basis for regulation of biologics, human tissues and blood, by first developing and evaluating technology, reagents, and standards to inform and improve chemistry manufacturing and controls. The second is to develop and assess nonclinical models and methods predictive of clinical performance with respect to toxicity and effectiveness. The third is improving clinical evaluation, pre- and post-licensure through use of big data, innovative designs and statistical analytical and modeling approaches. And last, but very importantly, to continue to prepare for future regulatory and public health challenges.

So as I mentioned we developed a research impact framework and we apply this to review all of our research programs, and we see this as having two levels. One is a portfolio level review, which the RSC undertakes, and the other is at the project level review, which is done through

the office review, and we obviously want to make sure our research is aligned with center and office goals and objectives, we want to make sure that we have the expertise to support our review, capability, both current and anticipated, and to maintain an agile set of internal capabilities to address the unexpected urgent public health needs.

We also want to make sure that our research is making a unique contribution, that we're using our scientific expertise to really enhance our ability to fulfill our regulatory mission, and of course, very importantly, always scientific merit and productivity are critical components to evaluating the research.

So, starting in FY17, one-fourth of all our research programs, as well as any new project proposals, go through an internal peer review research program. But all programs, every year, are reviewed at multiple levels by the supervisor division and office, through an online reporting tool called the annual research report. And then, as I mentioned, the regulatory science council performs a portfolio review, and again, we apply this research impact framework.

The PI submits to this online research reporting database, at the program level, information, overview, self-identifying relevance to the various goals at the

center and FDA level. If it's relevant to counterterrorism or other regulatory-specific areas. Importantly, regulatory accomplishments that have come out of the research. Staffing, collaborators, various compliance information, and then also things like select agent attestation and dual use research of concern attestations. And obviously, we collect publications, presentations. Other relevant output might be including things like employee invention reports, patent applications, and so on.

At the project level, we request a summary, the background, expected outcomes, and again, self-identifying the relevant office goal and objective. Each project should be organized around one to three specific aims, which should then be further defined through an explanation of their experimental approach, and then each year that's updated with the progress, the plans, and the anticipated results. Staff, budget, compliance information, again, and then what has been the regulatory and scientific impact, technology transfer information, and publications and other forms of dissemination is also collected at the project level.

In addition to that annual review, we also do cyclic peer review of every principal investigator, every four to five years, and again, this site visit that's done by external peer reviewers is a very important component of

that. The report that you're going to be reviewing today becomes part of a larger package that includes also information about the individual's regulatory contributions that goes to an internal committee for promotion and evaluation of the researcher reviewers.

The way things work is that there's two pathways for research scientists, both starting in temporary positions, either as a senior staff fellow or a staff fellow. The senior staff fellow is a principal investigator level, meaning that they are an independent scientist, with independent resources. And similar to academia, they're given up to seven years to go through at least one site visit and that recommendation, then, goes to the CPERR for another independent evaluation.

The same for the staff fellow or visiting associate. These are support scientists who may also go through a similar pathway for evaluation. At any point, they can also apply through an open competition to become permanent principal investigators or staff scientists. Again, principal investigator being independent, staff scientists being support scientists.

Today, what you're looking at is the draft report that was generated at the end of the site visit. You have before you three options. You can accept the report, amend

the report, or reject the report and send it back to the site visit team.

Once it's approved by the full advisory committee, then that report is important for a number of things, as I mentioned. It goes into that larger internal package for the CPERR review, the PIs take the advice that they receive through these reports with regard to the specific research they are doing very seriously, and of course management takes into account your recommendations with regard to resource allocation decisions.

I'll stop there and answer any questions. And just a reminder that the actual report won't be discussed until closed session, but general questions, I'm happy too entertain at this time. Thank you.

DR. PRIOLA: Thank you, Dr. Wilson.

For those on the phone, if you have questions, you can email Bryan and give him a heads-up, or, if you haven't done that, just please state your name first and then ask your question. Are there any questions from any of the participants?

Okay, if not, we'll move on to the next presentation. That's Dr. Atreya, who is the associate director of the Office of Blood Research and Review, and he'll give us an overview of their programs.

Agenda Item: Overview of OBRR Research Programs

DR. ATREYA: Thank you, and good morning, everybody. I will briefly give you the overview of our office, how it functions and -- we have this office organizational chart. Our office director, now the acting director, Dr. Nicole Verdun, and the associate acting deputy director is Hira Nakhasi. We have an associate director for policy, which is Jennifer Scharpf, and myself as the associate director for research.

Under this office we have two divisions. One division is the Division of Emerging and Transfusion Transmitted Diseases. Under that division there are four branches. One branch is the product review branch, and there are other three branches, are the laboratories where the research programs are stationed. And then the other side, we have another division that is the Division of Blood Components and Devices, and under that division we have two branches, which are completely review-related, and then there are two laboratory branches, which are not under review today.

Our office mission is to ensure the safety, efficacy, and availability of blood products and blood components. This is achieved through the regulation of blood and blood components for transfusion, and plasma for fractionation, devices used in manufacture of blood and

blood components, blood collection containers and additive solutions, plasma for volume expanders, oxygen-carrying solutions, donor screening tests and confirmatory tests for transfusion transmittable infections, and pathogen reduction devices. Also, we do the diagnostic tests for human retroviruses.

Our office functions, to fulfill the mission, we establish policies and standards to ensure donor safety and the safety of the blood and blood products, the review of applications for investigational and commercial use of blood products, and related devices and retroviral diagnostics, perform establishment inspections, and assist the agency in regulatory compliance actions, perform health hazard evaluations and risk assessments of blood and blood products, and we engage in emergency preparedness, for example, Ebola and Zika virus outbreaks, as you all know.

And the global outreach and cooperation where feasible, and we also organize scientific workshops on timely topics that are important to our office, and as part of the office functions we also have a robust program, as Carolyn mentioned, that is the research programs, and we conduct research to facilitate the development, manufacture, and evaluation of blood products and retroviral diagnostics.

The vision for our research in the office is to support the FDA's 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 a regulator is most contributory, and we have the provision of an infrastructure for investigation of product limitations and failures and advancing innovation in research areas that enrich the FDA's regulatory science base.

Our resources to do all these jobs, we have subject expertise like virology, retrovirology, bacteriology, parasitology, prions, cell biology, immunology, biochemistry, and physiology, and we have currently 16 investigator-initiated programs located under those two divisions which I mentioned briefly a couple of slides ago.

Our programs are mostly funded by both intramural research programs, that is, funded by CBER/FDA, and also some of the PIs have applied for external sources like NIH, NIAID, NHLBI, DoD, and some CRADAs with industry, where it is possible.

To do this research program, we do have, as Carolyn Wilson mentioned, each office has their own goals and objectives, and our office's research goal, there are

two. Number one is assess and promote the safety and effectiveness of transfusion products and related devices and technologies. The objectives under that goal are to evaluate ex vivo stored platelets or red cells, and the safety and efficacy, toxicokinetics and development of biomarkers of product quality, including omics-based approaches and to study the microparticle-associated toxicities.

Evaluation of the safety and effectiveness of oxygen-carrying solutions, platelet-like products, and related biologics. Development and evaluation of reference panels for molecular typing methods for blood groups and HLA antigens. Facilitate development of pathogen reduction technologies applicable to especially whole blood and blood components.

Goal two is to assess and promote safety and effectiveness of transfusion transmitted infectious disease agent donor screening and supplemental tests, and retroviral diagnostics. Under that, the objectives are to the evaluation of screening and confirmatory technologies for detection of TTID agents for assurance and enhancement of blood safety, development and evaluation of reference panels for screening and confirmatory test for TTID agents and retroviral diagnostics, facilitate preparedness for blood safety from emerging infectious agents and other

pathogens of global significance through investigations of mechanisms of transmission and pathogenesis.

Our office also involves with global outreach. Our staff participates either as a member or observer in many initiatives, for example, WHO initiatives -- under that, Collaborating Center for Biological Standardization, Expert Committee on Biological Standardization, Blood Regulators Network, Prequalification Program for Diagnostics. And also we interact with European Directorate for the Quality of Medicines and Healthcare, Blood Transfusions Sector and International Society of Blood Transfusion Working Groups on Transfusion Transmitted Diseases, Hemovigilance, and Global Blood Safety. And then FDA/EMA/Health Canada Blood Cluster. We participate in all these things.

Concluding remarks, briefly what I mentioned is I hope I gave the good impression that the research is integral to the mission of OBRR, CBER, and FDA, and our research facilitates product evaluation, development, and is aligned with, and fulfills, the regulatory science mission of CBER and FDA.

Thank you.

DR. PRIOLA: Thank you, Dr. Atreya. Are there any questions for Dr. Atreya from the committee?

Okay. If not, thank you, again. We'll move on to the next speaker. This is Dr. Nakhasi, and he's division director of the Division of Emerging Transfusion Transmitted Diseases.

Agenda Item: Overview of DETTD Research Programs

DR. NAKHASI: Thank you, and good morning. It's still 15 minutes until noon, and so it is still morning. So, what I will do is I will basically give you an overview of the division first, and our activities, and then I will summarize the outcome of the research programs which were reviewed at the December 6, 2017 site visit, and those three programs were under the Laboratory of Emerging Pathogens, Laboratory of Molecular Virology, and Laboratory of Bacterial TSE Agents.

When I am summarizing the PI's programs, we have some of the PIs, so if there are specific questions, I will direct them towards those particular PIs.

The next is basically the organizational chart, and since last time there has been some changes in the organizational chart, just to highlight now, because I'm playing the role of acting deputy office director in the division now. We have an acting director, Dr. Peyton Hobson, who was my deputy, and then also Dr. Anne Eder, who is going to be acting deputy director in that division.

The division is organized into three laboratories, which is researcher reviewer, and laboratories, and one completely regulatory branch. Today, from the three research laboratories, there are PIs whose programs are to be evaluated, and progress will be discussed today. Those are the Laboratory of Bacterial TSE Agents, and in that program Dr. David Asher's program and Dr. Luisa Gregori's program, was reviewed, and that I will review briefly, summarize the description of their program. In the Laboratory of Molecular Virology, Dr. Indira Hewlett's program was reviewed, and in the Laboratory of Emerging Pathogens, the two PIs in that group, Dr. Gerardo Kaplan and Dr. Maria Rios's programs were evaluated.

As Dr. Atreya mentioned, our research review program falls under the OBRR's research goal number two, which to assess and promote safety and effectiveness of TTIDs and donor screening and supplemental assays, as well as retroviral diagnostics. Having under that broad umbrella of the research goal, the mission of the Division of Emerging Transfusion Transmitted Diseases, which I will be referring to as DETTD, because it's a mouthful every time if I say that.

So is to plan and conduct research in the pathogenesis and the development of proof-of-concept for detection assays for bloodborne antigens, pathogens, such

as viral, which includes both the retroviral, hepatitis, and arboviruses, and parasitic agents, biodefense agents, and TSE agents. And then there is also a small program which is a CBER-wide unique expertise, about the biomarkers in vaccine development -- parasitic vaccines.

In addition, the mission of the division is to proactively ensure the safety of blood through regulation of these tests through blood screening and retroviral diagnostics; evaluate these tests through submission from the industry through BLAs, PMAs, 510(k)s, INDs, and IDEs, evaluation of new technologies for rapid and multiplex screening of blood supply, and to develop policies, guidance policies, for both donor screening and developers of the tests.

In addition, the mission of the division also is to develop reference material for lot release, which is used for the validation of these assays. In addition to that, we also collaborate as a WHO collaborating center to help them in developing international standards for infectious agents. We also do investigational tests, through inspection or the consultation to other components of the agency.

And finally, the mission includes the scientific and technical advice to other agencies of the government, such as CDC, DoD, Department of Health and Human Services,

and which is attained through the Blood Product Advisory Committee or through the Department of Health and Human Services advisory committee on blood, organ, and tissue safety. We also act as a liaison with many of the blood establishment committees and device manufacturer committees, and we, as I mentioned earlier, we are a WHO collaborating center for IVDs. And we also are involved in the public health service subcommittee for horizon scanning for emerging and reemerging bloodborne pathogens.

As mentioned earlier, our really portfolio is the safety of the blood supply, and this is just to give you an idea what we are talking about. There are almost 13.2 million donations are screened every year -- this is 2015 data -- from 6.8 million donors, and some of them, usually two-thirds are repeat donors and one-third are first-time donors.

You can see from that, after screening the blood, there are many of these components -- how many components are transfused. There's an enormous amount of the blood screening going on. That is important because how does that screening impact the impact on the transfusion transmission infection? This slide is really to highlight -- it's an old slide, but it's a very important slide -- that before the testing was instituted in screening the blood donors, you can see the risk per unit was much higher

for at least three agents, which at that time, HIV, HBV, HCV, and since then you can see how many agents have been coming through. And now, where we are currently, the risk has significantly dropped quite a bit. That itself speaks for our efforts in the blood safety arena.

This is just to reiterate that point, that currently we have test for many of these agents, retroviral, HIV, HTLV. We have tests for hepatitis, HCV, HBV. Arboviruses, West Nile, Zika, parasitic agents, T. cruzi and babesia, syphilis, CMV. In addition -- these are all approved tests -- and in addition, we also are screening using investigational tests, cobas(?) Zika, NAT assay, as well as babesia NAT assay.

Now, what are the challenges for the blood safety and availability? There are many challenges, including, first of all, reemerging pathogens, such as HIV variants and arboviruses. As many of you know, every time we hear something, or the new thing is coming up, as you must have heard from yesterday's NPR news, we now have some called Keystone virus, which was found in a teenager in the Florida area, and it is some kind of a negative single-stranded RNA virus, and it has been circulating wild in that area for a while, but now they have found that in a person.

When we have emerging pathogens, such as biodefense agents and you heard recently, there's a Nipah epidemic going on in southern part of India, and Ebola is again flaring up in some parts of Africa. In addition, in this country, we have tickborne pathogens on the rise, especially with the tickborne diseases such as Anaplasma, Borrelia, Rickettsia, Ehrlichiosis, and TSE agents. And then addition to that we have neglected tropical diseases, which are always on the rise, such as leishmania, malaria, T. cruzi, Human African Trypanosomiasis.

Then in addition to that emerging and reemerging pathogens, now what are we? We still lack assays for some of these pathogens, either individually we can screen them, or multiplex. Pathogen reduction methods are not approved for all the products. We have lack of confirmatory assays, and then we have also quite a bit of potential impact of trial based deferrals based on the exposure on the blood supply.

And also, there is many things which we do not understand about these pathogens, i.e. pathogenesis of these, how they are transmitted through the blood.

Now I just want to give you a brief quick scenario here. The DETTD mission-relevant regulatory research going on in the division, we have studies on pathogenesis of these viruses. We are evaluating new

technologies simultaneously. You will hear some of the later presentations. Studies on the evaluation -- my presentation, in my talk towards the end, which will be summarizing from several PIs, and we have some -- we are working on the safety and blood and blood products for risk of transfusion transmitted malaria, babesia, leishmania, and studies and diagnosis and vaccine efficacy of Ebola virus, and developing methods to improve the safety detection for the T. cruzi.

I just put it here. It's like the examples of the mission relevant research publication. I don't want to, you know, go one by one, but for your purpose, you can look at the slides at your own leisure, but there is a -- the point here there is a lot of significant mission-relevant research going on, and these publications are in high impact journals being published. So therefore, it makes -- it has made quite a bit impact.

In addition to the publications, we also are developing as I mentioned earlier, our mission is to develop and evaluate these reference reagents, and there's a list of all these reference reagents, which are used by the industry as well as internally for validating these assays which are being approved or cleared.

All this work is being done in the division by ten principal investigators, and last year with the support

of other staff and there are -- last year, there were 41 publications and the funding came mostly through the intramural as well as outside funding as Dr. Atreya mentioned.

People are seeking from outside -- outside means in the agency as well as through CRADA, approximately $4.1 million. In addition to getting the money, you can see the staff is really, has last year reviewed around more than 450 publications, which includes from all sorts of in all flavors, BLAs PMAs, and supplements and 510(k)s.

Now I will just focus on in the rest of the time, I'll focus on the research programs which were presented at the December 6 meeting, and the three -- the PIs work, which is Indira Hewlett from Laboratory of Molecular Virology, David Asher and Luisa Grigori from LBTSEA, and Maria Rios and Gerardo Kaplan from LEP.

Dr. Hewlett's program, in a summary, focuses on two areas. One is the HIV genetic diversity diagnosis and pathogenesis, and also developing novel technologies, which include nanotechnology, microarray, Nextgen sequencing for HIV and bloodborne pathogens.

First, the HIV genetic diversity studies she has been able to standardize the PCR new gen sequence assays and validation for the HIV characterization. She has developed point of care nanopore sequencing assays and she

can read quite in those assays, you can quite a bit read up to 9 kb sequences, and using that methodology, she has been able to now distinguish between the co-infection, dual viruses, and in the samples and some -- she also in future use in-house Sanger sequencing, MiSeq, et cetera.

Also, because the important thing is not just she's trying to do the sequencing, but the important thing is that there are these HIV and retrovirus, there's quite a bit diversity, heterogeneity and recombination things all the time going on. So it's important to understand what those are, because some of the -- it may impact assays, which are being approved now, whether all those assays are picking up those in each variant or recombinant.

Using those samples, she is also planning to develop reference reagents because those are important for validating those assays.

In the area of nanotechnology diagnostics, she has developed a highly sensitive p24 antigen nanoparticle assay that can detect all major subtypes and recombinants, and she is now in the process of technology transfer from bench to assay to lab on chip platform. This assay's format will be used to develop assay based on novel host biomarkers.

Now I focus on the -- again, if you have questions, Dr. Indira Hewlett is here to answer some of

those questions if you have those questions. Then the other laboratory which was reviewed at that time, and the PIs in that laboratory, LBTSEA, and then Dr. David Asher's program, as well Dr. Luisa Gregori's program.

Dr. David Asher's program has two objects. One is to rapid postmortem detection of abnormal prion proteins in human brain tissue. He has developed a rapid sensitive and specific detection in small samples of human CJD brain by ELISA method, and confirmed by rapid testing of postmortem frontal lobe biopsies and optic nerves of vCJD infected monkeys.

Also, his lab has been over the years involved and made significant contribution in the areas of these cell substrates which are used for other making vaccines and other things, whether those in BSE agents are present in those cell lines, and his efforts over the years have shown luckily those cells resist infection from these three potentially contaminating TSE agents, sporadic CJD, variant CJD, and BSE.

Dr. Luisa Gregori's research is focused on developed one to reference reagents for the vCJD, because there are no assays and her efforts are really very important to develop those reagents could be used to validate these assays in future. Also, develop a model to demonstrate the infectivity by transfusion transmission.

So what she has done in the -- she has developed a macaque model where she has infected the macaques with the infected brain and over a period of time, some of these macaques develop disease. She has collected the blood from different time periods, and using those blood samples which could be used as panels at the same time she is also developed and using those samples to validate the assays which are already research type of assays to see whether, how good those assays are.

Then she is going to continue to work on the transfusion -- she has taken this blood from these infected macaques and transfusing them into naïve macaques to see when and how through the blood transfusion the disease is developed, and again, as you know, many of you know that it is not a -- it is a very slow process.

She is also really addressing another regulatory question, which is basically that there was some issue with the heparin manufacturing, and maybe the contamination with BSE agents and her laboratory has developed an assay which can detect these heparin in those -- sorry, the BSE agents in the heparins.

Now, the Laboratory of Emerging Pathogens, the two PIs who were reviewed were Dr. Maria Rios and Dr. Gerardo Kaplan. Their research programs, Dr. Maria Rios's program also has two objects, one is the genetic evolution

and pathogenesis of flaviviruses. She has studied the molecular epidemiology for West Nile, dengue, and Zika, and again, to study the genomic diversity and monitoring these if there are variants over a period of time and how they impact the assay performance.

She has also worked on improving the detection of early infections of these arboviral assays, arboviral infections, and she has developed -- while studying the pathogenesis, she is also developing biomarkers of infections so that they can be used as early detectors.

In addition, many of the pathogens -- many of these arboviruses, they bind to various cell, blood cell types, and when we measure these pathogens, usually in a blood screening assay, it is usually plasma or serum, and therefore, and many of them, that if they are, you know, cleared from that, but they are -- some of these pathogens can stick to some of these red cell, like for example some of these cells, pathogens and red blood cells, platelets, and she is trying to understand whether that in fact binding to those cells really causes infection and how important that is in the pathogenesis.

In addition to that, she has been very much doing a lot of reference reagents she has developed for over the years for West Nile, chikungunya, dengue, Zika, and for dengue, her panel was used as a WHO international reference

reagent and recently approved for that. So that's her contribution in not only in the office, but also internationally. She also has a program for developing the reagents for blood group antigens and genotyping, and she has now developed, characterized, DNA from many of these cell types, and using those as a marker and because many of the markers are used nowadays who could be used for future detection of blood grouping agents. We have serological markers, but then these are the DNA markers.

Lastly, but not the least, Dr. Gerardo Kaplan's program, which is again two sets of studies, one is the cell entry, pathogenesis, vaccines and diagnostics of hepatitis A viruses, and he has one -- he was the one who originally discovered the hepatitis receptor, A receptor, and then how he then worked on to how that interaction of hepatitis A and receptor results in the modulation of immune response, and then also he has recently confirmed the functional HAV receptor by using CRISPR technology, and also he addressed the regulatory question where one of these immunoglobulins, which had low HAV potency because many of them are user therapeutic, and then defined -- identified what the cause of that was.

His program also is involved in looking at the cell entry pathogenesis vaccines and diagnostics of filoviruses, and he has developed this whole program

started when the Ebola crisis started, and his laboratory was very helpful in developing BSL Ebola virus fluorescence reduction neutralization assay based on the recombinant VSV.

He developed a filovirus candidate vaccine based on the extracellular domain of glycoprotein fused to the Fc segment of the human IgG. He also evaluated antibodies by BSL-2 ELISA and in samples from NIAID filovirus preclinical vaccine trials, and he participated in WHO collaborating studies to evaluate Ebola virus antibodies and antigen international standards.

With that, I think I will stop here and I want to thank you for your attention, and if you have questions, I'm here to answer those questions.

Agenda Item: Questions for the Speakers

DR. PRIOLA: Thank you, Dr. Nakhasi. Are there any questions from the committee for Dr. Nakhasi on the research programs he described, or on the mission of DETTD itself?

It doesn't appear to be. Thank you very much, Dr. Nakhasi.

So before we move on to the open public meeting, are there any questions in general for any of the speakers that we have heard so far?

(No response.)

Okay, Bryan, should we move on to the open public hearing?

Agenda Item: Open Public Hearing

MR. EMERY: We can move on to the open public hearing. I will look out in the audience and ask if there's anyone in the audience that would like to speak during the open public hearing, because we have not had anyone that has been in touch with us that has requested ahead of time to speak during open public hearing.

I see no one that wants to speak during open public hearing at this time. So I will turn it back over to you, Dr. Priola, to move to the next section.

DR. PRIOLA: Thank you, Bryan. So I guess we are going to move on then to the closed committee discussion, and my understanding is that the webcast will go blank and this will just be with the people in the room and the members of the committee on the phone. Is that correct?

MR. EMERY: That is correct. When we go to closed session, we will empty the room of non-participants and it will not be webcast until later this afternoon when the second session opens up.

DR. PRIOLA: Okay, let's move on to do that. Can you let me know when we're okay to go ahead and start the discussion there?

DR. STRAMER: This is Susan Stramer, and I just wanted to let you know that because I'm the industry rep, I will drop off at this time. I thank the speakers. It was very informative. So I just want to say that I recognize the importance of research towards the FDA's, CBER's and OBRR's mission.

DR. PRIOLA: Thank you, Susan. You will call back in for the topic II after lunch?

DR. STRAMER: Yes.

MR. EMERY: Thank you, Dr. Stramer.

(Break)

AFTERNOON SESSION

Topic II: Review of the Research Program of the Hemostasis Branch (HB), Division of Plasma Protein Therapeutics (DPPT), Office of Tissues and Advanced Therapies (OTAT), Center for Biologics Evaluation and Research (CBER)

MR. EMERY: Good afternoon, everybody on the phone. We are going to be starting the committee meeting at this time, the afternoon session, topic II on the agenda.

We can do introductions here in the room first and then introductions on the phone. And then I will give some brief announcements before we get started with the second session.

DR. WILSON: Good afternoon, again. Carolyn Wilson, the associate director for research, CBER.

DR. BRYAN: I'm Wilson Bryan. I'm director of the Office of Tissues and Advanced Therapies.

DR. ANATOL: Hi, Rachal Anatol, deputy director, Office of Tissues and Advanced Therapies.

DR. EPSTEIN: Suzanne Epstein, associate director for research, Office of Tissues and Advanced Therapies.

DR. GOLDING: Basil Golding, division director, OTAT, DPPT, Division of Plasma Protein Therapeutics.

DR. LEE: Tim Lee, branch chief of the hemostasis branch, DPPT, OTAT.

DR. KIMCHI-SARFATY: Chava Kimchi-Sarfaty, principal investigator, DPPT, OTAT.

DR. OVANESOV: Mikhail Ovanesov, principal investigator, DPPT, OTAT.

DR. SARAFANOV: Andrey Sarafanov, principal investigator, OTAT, DPPT.

DR. SAUNA: Zuben Sauna, principal investigator, DPPT, OTAT.

MR. EMERY: My name is Bryan Emery, lieutenant commander. I'm the DFO for this committee, and I also want to recognize Prabha Atreya, my division director, and one more person, who is about to --

DR. MARKS: Hi, Peter Marks, center director for the Center for Biologics.

MR. EMERY: Okay, I'm going to do a roll call and introduction kind of at the same time, so, Dr. Priola, if you would introduce yourself.

DR. PRIOLA: Yes, this is Sue Priola. I'm a principal investigator at the Rocky Mountain Laboratories in Hamilton, Montana.

DR. LEITMAN: This is Susan Leitman. I'm director of the Medical Research Scholars Program at the National Institutes of Health in Bethesda.

MR. EMERY: Dr. Jack Stapleton.

Dr. Meera Chitlur.

DR. CHITLUR: Hi, this is Meera Chitlur. I'm professor of pediatrics at Wayne State University, and the director of the Hemophilia Treatment Center and the Hemostasis Program at Children's Hospital of Michigan in Detroit.

MR. REES: Hi, this is Robert Rees, manager of the Blood Bank Licensing Regulatory Compliance Program for the state of New Jersey Department of Health.

MR. EMERY: Dr. Thomas Ortel.

Dr. Judith Baker.

DR. BAKER: Hi, Judith Baker, director, public health, for the Center for Inherited Blood Disorders, in Orange, California, and adjunct assistant professor at UCLA Division of Pediatric Hematology/Oncology.

MR. EMERY: Dr. Alfred DeMaria?

DR. DEMARIA: Al DeMaria, medical director of the Bureau of Infectious Disease and Laboratory Sciences at the Massachusetts Department of Public Health, and the Massachusetts state epidemiologist.

MR. EMERY: Dr. Roger Lewis?

DR. LEWIS: Roger Lewis, I'm the chair of emergency medicine at Harbor-UCLA Medical Center.

MR. EMERY: Dr. Amy Shapiro?

DR. SHAPIRO: Hi, Dr. Amy Shapiro. I'm the medical director and CEO of the Indiana Hemophilia and Thrombosis Center in Indianapolis. I'm a pediatric hematologist.

MR. EMERY: Dr. Andrei Kindzelski?

DR. KINDZELSKI: I'm Andrei Kindzelski, program director, blood division, NHLBI, NIH.

MR. EMERY: Dr. Martin Schreiber?

DR. SCHREIBER: Hi, it's Martin Schreiber. I'm the chief of trauma at Oregon Health and Sciences University, and I do research in novel blood products.

MR. EMERY: Dr. Richard Kaufman?

DR. KAUFMAN: Hi, this is Rick Kaufman. I'm the medical director for the transfusion service at the Brigham and Women's Hospital in Boston.

Agenda Item: Conflict of Interest Statement

MR. EMERY: Excellent. Thank you very much. Now I'll give brief messages.

Good afternoon. I am Bryan Emery, I'm the designated federal official of the Blood Products Advisory Committee. This is Joanne Lipkind, is the committee management specialist, and she can assist you with any needs at the tables located in the hall.

I would like to welcome all of you again to the 118th meeting of the Blood Products Advisory Committee held

in the FDA White Oak Great Room. Dr. Sue Priola is the acting Blood Products Advisory Committee chair for today. The CBER press media contact is Ms. Megan McSeveney, and Chanda Chhay is the transcriptionist.

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

For those members on the phone, please remember to place them on mute while you are listening in order to decrease any background noise here. For those around the table and in the audience, coffee, drinks, and snacks are out the doors to the right, as well as the restroom.

All committee topic discussion needs to be done in public forum and not in groups during the breaks. The FDA and public need your advice, thoughts, and expertise. The public and industry must stay behind the stanchions and in the audience area. Please do not enter into the FDA or BPAC committee table area. Please wait until the open public hearing designated time to make any remarks, using the center aisle microphone.

That ends the reading of my comments. I will turn the meeting over to Dr. Priola.

DR. PRIOLA: Good afternoon, everyone, and thanks for joining us for the afternoon session of the meeting of the Blood Products Advisory Committee. This session deals with topic II, which is a report of the site visit of the intramural research programs for the Division of Plasma Protein Therapeutics, and we're going to start with Dr. Suzanne Epstein, who is the associate director for research for the Office of Tissues and Advanced Therapeutics. She'll give us an overview of their research programs.

Agenda Item: Overview of OTAT Research Programs

DR. EPSTEIN: Thank you very much. I'll be giving an overview of OTAT and its research programs. OTAT was formed in 2016. It includes parts of the Office of Blood Research and Review, or OBRR, and all of the former Office of Cellular Tissue and Gene Therapies, or OCTGT. Products transferred to OTAT are plasma-derived products, including analogous recombinant proteins from OBRR, and then all the products that were in the former OCTGT. And note that products for transfusion remain in OBRR.

This shows an organizational chart for OTAT. Wilson Bryan is our office director, and divisions are shown. There are two divisions that have lab research: the Division of Cellular and Gene Therapies on the left, and the Division of Plasma Protein Therapeutics, next. As you

heard earlier, Dr. Dove Golding is the division director for DPPT.

The hemostasis branch that's under review today is in that division. Then we also have a Division of Clinical Evaluation and Pharmacology/Toxicology, a Division of Human Tissues, and Division of Regulatory Project Management.

Regulation in OTAT has to cover an extremely diverse portfolio of products and a wide diversity of pathways. We have many mature licensed products. We also have many exploratory investigational products that are in very early stages. Our sponsors are also diverse. Some of them are commercial, some are small biotech startups, and some are sponsor investigators. These include individual academics. So, some of these people have not previously sponsored INDs and need a lot of interaction.

We use a variety of designations for our products, to expedite development of those needed for serious conditions. These include the regenerative medicine advanced therapies designation from the 21st Century Cures Act, orphan products, fast track, breakthrough therapy, accelerated approval, and priority review. So, our work includes evaluating those requests.

In terms of the product portfolio, the hematology products will be described subsequently by DPPT leadership,

so I'm just going to mention for you briefly the other products in the office as context. We review gene therapies, cellular therapies, tumor vaccines and immunotherapy, tissue and tissue-based products, xenotransplantation, devices and combination products, cord blood, and donor screening tests. So, as you can see, it's both a diverse portfolio and includes some very active areas that are growing quickly.

The purpose of OTAT research includes staying ahead of the curve as these products and technologies evolve. For such a diverse set of products, it's impossible to have research related to every product. So, our strategy instead is to conduct work in key fields of science, and to stay in current at a time of rapid change and development in this field.

The benefits of the research programs include filling scientific gaps, dealing with barriers and problems encountered both by sponsors and by us in regulation, performing studies relevant to entire product classes or indications, while sponsors often focus on their individual products. We contribute information for policy development, and we make our results public, thus accessible to all sponsors, to advance the entire field, and we participate in communication efforts and public outreach.

To just briefly sketch the research areas, we have work in microbiology. This includes various virus categories, lentiviruses, adenoviruses, also viral safety of blood products, and pathogen detection and clearance in human tissues, blood, and plasma derivatives.

We have work in immunology, including immune responses to viral and plasma vectors, immune modulation by viruses, T cell biology, and immunogenicity of proteins.

Then cell and developmental biology and tissue biology, involving control of differentiation in animal models, cell fate and survival, stem cell biology, tissue engineering, and tissue safety. Quite a diverse area.

In cancer biology, we have studies of molecular markers, cancer vaccines, animal models, and immunotherapy.

Next, in molecular biology and biochemistry, we have studies of protein structure and function, expression, and regarding blood proteins, characterization of the proteins and their safety risks associated with adventitious agents, genetically engineered variants, mechanisms of action, international standards, and assays of biological activity.

Then there are some lab-based adverse event investigations related to hemolysis, thrombosis, and allergic reactions, and in biotechnology, we have expertise and also equipment in core facilities in genomics, flow

cytometry, transgenic animals, sequencing, bioinformatics, and in silico modeling.

Our researcher-reviewer staff members have a variety of responsibilities. They conduct research. They also, the same individuals, perform regulatory work. This includes IND and BLA review. It includes policy work, standards work, outreach, serving on inspection teams, and work in compliance, which can include court cases. They participate in CBER and FDA committees. They participate in the wider scientific community by reviewing manuscripts and grant proposals, editing, organizing, and helping organize scientific conferences, and they mentor their staff and postdoctoral fellows to support their professional development.

The output of our research programs include peer-reviewed publications of primary research data, review articles, editorials, symposium papers, regulatory papers, and also patent applications in some cases. Our funding is mainly from within CBER, but CBER scientists -- we're excluded from many outside grant sources. We do apply where eligible. And OTAT PIs have successfully obtained funding from various sources outside the FDA, as well as some of the agency-level grant programs.

To summarize, the OTAT research programs provide in-house, hand-on expertise in cutting-edge areas and

assays. They facilitate product development by addressing challenges encountered by sponsors and in regulatory review, and they help develop new approaches, policies, and guidance, to advance the field.

Thank you, and I'm happy to answer any questions.

DR. PRIOLA: Thank you, Dr. Epstein. Are there any questions from the committee members?

Okay, if not, thank you again, and we'll move on to the next presentation.

This is Dr. Dove Golding. He is division director of the Division of Plasma Protein and Therapeutics. He will give an overview of the DPPT research programs.

Agenda Item: Overview of DPPT Research Programs

DR. GOLDING: Good afternoon to everyone. You've just heard that I'll be presenting the research and the contexts of the research, the regulation, in DPPT. Before I go on to the slides, I just want to express my sincere thanks to the advisory committee and to the site visit team, for spending so much time and effort in evaluating our program. It's very important for us in continuing our research.

What I'm going to be talking about is division organization, regulatory responsibilities, and the research.

The division is as follows. The organization chart is in front of you. I'm the director. Mahmood Farshid is the deputy director. We have two administrative assistants, and then we have two branches. The hemostasis branch that we're reviewing today, which is headed by Timothy Lee, and the plasma derivatives branch, which is headed by Dorothy Scott.

In both branches we have four principal investigators. This just gives you an average idea of the time spent between research and review, and you can see for the PIs it's split 50-50. The same for the staff fellows; the ORISE fellows, or contract fellows, spent 100 percent of the time doing research, and we also have chemists and microbiologists that split their time 50-50 doing research and review. At any particular time, if there are deadlines to be met in the review area, those assume priority.

What is the regulatory function in our division? We look at a wide variety of applications and products and devices. The evaluation process of the products includes scientific review of the manufacturing processes, laboratory investigations, if they are needed, assay development, which is very critical, and developing standards for lot release. Without these manufacturing facilitating assays and standards, it's not possible for manufacturers to license their products.

In terms of surveillance, we are involved with inspections, adverse events, reports, and investigating product failures, and the legal framework of the Code of Federal Regulations, the PDUFA, the MDUFMA, and the Food, Drug, and Cosmetic Act, and multiple guidances.

The other tasks that we are involved in include policy and guidance documents, preparing and presenting at advisory committees, harmonization with other regulatory agencies at the ICH, which includes Japan and the Europeans and the Canadians. We have cluster meetings regularly with the EMA and Canadians. We also have liaison meetings with government agencies such as NIH and CDC, with industry, the Plasma Protein Therapeutics Association, and with patient groups, such as the National Hemophilic Foundation and the Immune Deficiency Foundation.

Communications include web posting and sending out letters. We also have workshops, almost on a yearly basis, to deal with evolving problems, to try and find paths forward. And from time to time we deal with citizen petitions.

The regulatory process -- how do we make decisions? This is based on scientific data showing safety, efficacy, and purity of the products, and the decision-making process includes internal review, and at times, presentation to advisory committees, multiple

meetings with manufacturers -- I've listed a few of them. Pre-IND meetings, pre-IDE meetings, the actual IND meetings, and pre-BLA, late-cycle meetings; there are also mid-cycle meetings, and so on. The meetings are held at regular time intervals depending on the progress of the manufacturing and the type of submission that is in now at the FDA.

What are the products that we regulate? This is the list of products that we regulate under the plasma derivatives branch. So, the first listed there, general immune globulins. These are given by different routes, IV, subcutaneous, IM, for primary immune deficiency, autoimmune diseases, such as immune thrombocytopenic purpura, and for neurological diseases such as chronic inflammatory demyelinating polyneuritis. Specific immune globulins are enriched for specific antibody specificities, for example, rabies, tetanus, botulinum, anthrax, snakebites, and I probably missed out a few.

In addition, we regulate certain enzyme inhibitors for hereditary deficiencies. For example, alpha-1 proteinase inhibitor is used as prophylaxis to prevent emphysema in people who are deficient, and C1 esterase inhibitor is used for hereditary angioedema.

I'm not going to go into detail for the hemostasis branch because Dr. Lee will do this, but just a

very quick summary. We regulate a whole host of coagulation factors for bleeding disorders, bypassing products for those patients that develop inhibitors, and then procoagulants, such as prothrombin complex concentrates for warfarin reversal, and anticoagulants, such as protein C, antithrombin III, and other hemostatic agents that are mainly used in surgery: thrombin, fibrin sealant, CryoSeal, fibrin sealant patch.

The scope of the research, again, this is a very brief summary. We look at the -- the research includes investigation of the efficacy of immune globulin products for different infectious diseases, such as flu, Ebola, Zika, hepatitis C virus, studies of the regulation of blood coagulation by coagulation factors VIIa, IXa and XIa; aggregates in protein products. Clearance mechanisms of proteins, particularly referring to factor VIII. Immunogenicity of protein therapeutics. Pharmacogenomic and codon optimization studies of proteins. Maternofetal transfers of antibodies. Assay and standard development. Counterterrorism and pandemic research, such as for influenza. And in the last five years, there have been 76 peer-reviewed papers published by the PIs in this division.

So I want to thank you for your attention, and I'm ready to answer any questions that you may have.

DR. PRIOLA: Thank you, Dr. Golding. Do any of you have any questions for Dr. Golding? Okay, if not, thank you very much.

We'll go on to the final speaker for this topic, and this is Dr. Tim Lee, who is chief of the hemostasis branch in DPPT.

Agenda Item: Overview of HB Research Program

DR. LEE: Good afternoon. As mentioned earlier, I'm going to give an overview of our branch, and research programs directed by the four principal investigators from our branch, and the progress that they have made since our last site visit in October 2013.

Here are all the research regulators in our branch, and my main responsibility as the chief of the branch is to oversee the regulatory activities in the hemostasis branch. I also supervise the research programs of Drs. Ovanesov and Sarafanov, when our group was in the Office of Blood Research and Review, and since the CBER reorganization in October of 2016, I also oversee now the research programs of Dr. Kimchi-Sarfaty and also Dr. Sauna, who previously reported to Dr. Golding.

Our principal investigators and staff scientists, working with them, are involved in both research and regulatory activities. Depending on the volume of regulatory submissions, the proportion of workload for

these two activities can vary anywhere between 50 and 80 percent.

In addition to our research regulators, we also have five fulltime regulatory reviewers, who spend 100 percent of our time in regulatory activities. In our branch we regulate about 50 products, which include coagulation factors that are manufactured either from plasma or by recombinant DNA technology. And in addition, we regulate factor VIII/vWF complexes, and other products include anti-inhibitor coagulating complexes for the treatment of hemophilia patients with inhibitors, hemostatic agents, anticoagulants, and reversal agents for anticoagulants, such as Kcentra for the reversal of vitamin K antagonists.

Our regulatory responsibilities include a review of applications from manufacturers during the various stages of product development, from investigational products using clinical trials to new drugs poised for marketing, and a substantial amount of our time in review involves those submissions that report manufacturing changes for already-licensed products. And our staff members also serve as product specialists during the inspections of manufacturing facilities. Depending on the demand from the field, and also the submissions, each of our staff members can be participating in as many as two to

three inspections per year. We support them either on site or by phone.

Currently, most of the product testing activities are carried out in Dr. Ovanesov's laboratory, specifically for the identification and monitoring of procoagulant components in immunoglobulin products for our sister branch. Other regulatory activity involves a review of biological product deviation reports, for which we assess the risk involved as a result of deviations experienced during product manufacture. We also assess the adequacy of the responses to correct and prevent similar deviations from recurring.

We also participate in working groups for the development of policy and guidance documents, concerning the various aspects of the regulation of products, and, as mentioned earlier, much time is also spent in activities aimed to provide advice to sponsors for the preparations of studies and also preparations of the applications for future submissions. These activities involve the review of briefing documents on their requests, and discussions with our colleagues internally and also with the sponsors externally, and the preparation of meeting summaries.

Between the two site visits of 2013 and 2017, our branch has completed the review of 19 original biologics license applications, and among the approvals are some

first of its kind products. For example, Tretten is the first recombinant factor XIII concentrate; Eloctate and Alprolix are the first FC fusion proteins of coagulation factors VIII and IX respectively; Idelvion is the first albumin fusion protein with factor IX; Adynovate is the first PEGylated factor VIII product; and Rebinyn is the first glycol-PEGylated factor IX product.

And also, the agency has licensed the first recombinant analogue for von Willebrand factor, which is Vonvendi, on the list. And recombinant porcine factor VIII, Obizur, on the list. We have also licensed the first plasma-derived factor X product.

In addition to the review of the original applications, we have also reviewed hundreds of submissions related to existing BLAs, and the INDs and their associated amendments. As mentioned earlier, we also participated in the four years, several pre-license inspections and also supported some CGMP biennial inspections, which are headed by our colleagues in the Office of Regulatory Affairs. And also, we participated in international calibration studies for reference standards.

We are looking forward to reviewing emerging products, that include new PEGylated or fusion proteins or coagulation factors. As you know, these products are developed with the hope that these changes might modify the

PK and/or PD of the proteins, and improve the treatment of congenital bleeding disorders. Other products that are on the horizon are being developed to treat arterial thrombosis and thrombotic thrombocytopenic purpura.

I would like now to briefly summarize the research activities in our branch. Just as our regulatory activities cover the different stages of product development, our research programs also address issues at different phases of the product lifecycle. And also, you will see that under the theme of mission-relevant research programs, these studies also aim to answer some basic questions in science.

Dr. Chava Kimchi-Sarfaty's research interest has been on understanding how synonymous and nonsynonymous mutations affect the function and structure of protein, which she translates into a research program that develops strategies toward more effective treatment of blood-clotting disorders. Her research program aimed to develop scientific expertise to understand the biology and physiology of biological products, specifically the outcome of mutations or variations in therapeutic proteins.

And also, to facilitate the development of safe and effective biological products by providing the public with prediction tools to estimate the consequence of changes in coding sequence of therapeutic proteins during

product design and characterize the biology and functionality of ADAMTS13 and von Willebrand factor in the population and in specific disease states to further the recognition of efficacy and safety implications of these therapeutic proteins in patient-specific contexts. For example, pediatric congenital heart disease, and sickle cell disease.

Her first project asks the question, when and how do synonymous variants impact protein biogenesis? Chava and her colleagues approach it by examining the effect of factor IX nonsynonymous and synonymous mutations on splicing. In the process they have improved the tools to identify which messenger RNA and protein domains are more favorable or are less favorable to manipulation.

Also, they identify correlations between experimental ribosomal profiling data and in silico predictions through statistical analysis.

Since our site visit in October 2013, Chava and her colleagues have completed several projects, as well as continued to study several others. They have established single-gene copy cell lines with a defined integration site to study the effects of codon optimization under a controlled genetic environment. They've also designed new bi-codon usage tables, and they continue to develop a hemophilia-specific prediction tool to estimate the

consequence of synonymous and nonsynonymous mutations and are validating this tool.

They are studying the effect of synonymous polymorphism in ADAMTS13 on protein expression, conformation, and function. They are examining the effect of factor IX, ADAMTS13 bi-codon optimization on protein expression, conformation, and function.

They are also examining various codon optimized factor IX altered antigen processing and factor IX antigen presentation, using in silico and in vitro tools. They are testing codon-optimized factor VIII, using ribosome profiling to develop better algorithms for the optimization of factor VIII sequence. They are also developing codon usage tables for a variety of healthy and cancer tissues and primary cells in order to better understand tissue-specific codon usage bias.

As for her second project, she is investigating the role of ADAMTS13 in different hematologic conditions. They approach this by first developing assays to measure the level of expression and the activity of ADAMTS13 so that they can examine ADAMTS13 expression and function in nonactivated and activated primary cells. They are also interested in understanding the biology and the roles of ADAMTS13 and vWF play in sickle cell disease.

Moving on to the program directed by Dr. Mikhail Ovanesov. Mikhail has a long interest in the regulation of blood coagulation, specifically by coagulation factor VIIa, IXa, and XIa. And in the process, he and his colleagues have developed tools to address some of the basic issues related to the regulation of products under our purview, such as standardization, harmonization, and monitoring of product quality.

In standardization, biological reference standards for coagulation factor activity and antigen support the accurate potency assignment, detection of harmful procoagulant impurities, and diagnosis of bleeding disorders.

With harmonization we can ensure analytical procedures, give comparable results in different laboratories, and with better understanding of the mechanisms of action of hemostasis and thrombogenicity of some coagulation factors, we can better monitor and control their potency and their level as a therapeutic protein or as product impurities.

Mikhail and his colleagues have participated and will continue to participate in collaborative studies for the assignment of potency and antigen values, to several new replacement international standards. In the interest of time, I'm not going to go into details about the various

coagulation factor international standards, but instead we will go to discuss a longstanding situation related to the discrepancies observed between different coagulation factor assay methodologies.

Effective and safe dosing and monitoring of coagulation factor products requires the reconciliation of the clotting factor potency assigned on the product label with the activity recovered in post-infusion patient plasma samples. Discrepancies in activity values between the potency assay and the PK assays for genetically and chemically modified long-acting coagulation factors can lead to the potential of overdosing or under-dosing of the patients.

Mikhail and his colleagues are in the process of investigating the assay conditions to understand discrepancies and also to support the development of assay harmonization approaches for long-acting products. With the study of mechanisms of action, for factor VIIa, there have been over a dozen genetically and chemically modified factor VIIa variants entering the product development pipeline in the last few decades. His laboratory has used a hemophilia A mouse model and several assays for VIIa antigen, for factor VIIa activity and thrombin generation to study the mechanisms of action of these factor VIIa

variants in an attempt to predict the duration of the action in vivo.

With regard to the factor XIa mechanisms of action, which is related to the adverse events observed in the use of immune globulin products, they are investigating the molecular mechanism that block factor XIa inactivation by plasma inhibitors that allow the activated factor XIa activity to remain in the blood for 24 hours or longer.

Next, we go to the program directed by Dr. Sarafanov. Andrey's interest has been always in the catabolism of factor VIII, and he translates that interest into the investigation of the mechanism of clearance of factor VIII when it is either complex with vWF or free from vWF.

Also, another project of his is in the characterizations of inactive proteins that are present in the currently licensed factor VIII products. As it is, understanding the mechanisms of interactions between factor VIII, factor VIII/vWF complex, and their clearance receptors, facilitates the regulation of long-acting factor VIII and vWF products.

Better characterization of product impurities will improve product quality. So, taken together, the outcome of his research will improve the quality, safety, and efficacy of products for the treatment of hemophilia A.

Since the 2013 site visit, Andrey and his colleagues have further characterized the interactive sites between factor VIII and its clearance receptors -- low-density lipoprotein receptors, LDLR, and also LDLR-related protein. They have also proposed a dynamic bivalent model of interaction of factor VIII with LDLR. This could be a new mechanism of action for biomolecular interaction, particularly relevant to receptors from the LDLR family and their ligands. They also perform initial mapping of the LRP sites for the binding of von Willebrand factor.

In studies in line with Harvard's research interests, Andrey's group have expressed and characterized a codon-optimized B-domain deleted factor VIII. They demonstrated an approach to characterize new products based on codon-optimized factor VIII, and they also proposed an explanation on the root cause of the atypical assay discrepancies with transgene factor VIII in the ongoing clinical study for gene therapy for hemophilia A.

For the characterization of impurities in factor VIII products, they have optimized conditions for running an affinity column, and they have also studied the condition for using hydrophobic interaction column to separate factor VIII protein from its impurities, inactive protein impurities.

Dr. Zuben Sauna has built his research program on the understanding of immunogenicity of proteins from the ground up, when he first joined in our group and came to realize that tools to assess the risk of immunogenicity are lacking and should be developed. Because immunogenicity compromises the safety and/or efficacy of protein therapeutics, and it's a priority for regulatory agencies. Also, the human and economic cost of immunogenicity to patients, their caregivers, and the healthcare system are considerable.

Immunogenicity adds to the risk and costs associated with drug development. The lack of predictive tools might discourage industry from developing products to treat rare diseases. His research goals are then to identify the pharmacogenetic determinants of immunogenicity, to develop in silico, in vitro, and ex vivo tools for nonclinical predictions of immunogenicity, and to develop tools to assess neo-sequences in bioengineered protein therapeutics for immunogenicity risk, and to develop strategies to deimmunize protein therapeutics.

He has taken a logical approach to develop his research program. Zuben used computational methods on existing clinical data to propose that sequence mismatch between endogenous and infused proteins and affinity of the foreign peptides for an individual patient's HLA molecule,

could predict immunogenicity risk. He then used a genotype cohort of hemophilia A patients to demonstrate that the the paradigm in A can be used to assign personalized immunogenicity risk, and based on the outcome from 2, he proposed that neo-sequence-HLA affinity in engineered therapeutic proteins could be risk factors for immunogenicity. He then demonstrated that the paradigm described in 3 is valid.

Since the 2013 site visit, Zuben and his colleagues have developed algorithms and experimental methods for nonclinical immunogenicity risk assessment. They have developed a mouse model to study the immune consequences of Fc-engagement with the numerous Fc-receptors found in mammals. And they've demonstrated by using a post-hoc immunogenicity assessment of a recombinant factor VIIa analog, that the sequences introduced were strong T-cell epitopes.

Using an MHC associated peptide proteomics, they've identified factor VIII-derived peptides on patient cells, which can be used to test hypotheses from clinical studies showing different prevalence of inhibitors among factor VIII product classes. In another project they've developed assays to identify preexisting antibodies to Cas9, which is used for genome editing, and they've

established prevalence of anti-Cas9 antibodies in the human population.

That will be my overview of all the research programs in HB, and these research programs in our branch were reviewed by the site visit committee in November of last year, 2017. During the site visit, we asked the site visit committee to evaluate the relevance of our research program to the mission of the center, and also the scientific relevance and soundness of the approach taken to answering the posed research questions.

In addition, the division also put forth several personnel actions for the committee's recommendation. The general conclusion of the 2017 site visit are that the committee was satisfied with the progress made in each of the research programs, and also the committee was in broad agreement with the direction of the research programs in our branch. In addition, the site visit committee supports the recommendations for personnel actions put forth by the division.

With that, I would like to end by first expressing my gratitude to everyone in the hemostasis branch for all the good work that they have done, and then on behalf of the branch, I would like to thank the site visit committee for their generosity in sharing their time and expertise. We appreciate their constructive criticisms

on our research programs, and their suggestions on how to improve them.

We would also like to thank the BPAC members for your interest in our work and your support, and I would also want to thank our supervisors and colleagues in the division, in our office, and also in our center, for their continued encouragement, guidance, and support for what we do, be it in research and regulation.

Thank you, and I would like to answer any questions if you have.

DR. PRIOLA: Thank you, Dr. Lee.

Agenda Item: Questions for the Speakers

Does the committee have any questions for Dr. Lee?

If there are no questions, I'll open it up in general to questions, once more, for all of the speakers, before we move on to the open public hearing.

Okay, if not, thank you very much to all the speakers, and Bryan, should we move on to the open public hearing?

Agenda Item: Open Public Hearing

MR. EMERY: Yes, we can move on to the open public hearing at this time. I'm looking at the audience, and I don't see -- is there anyone that would like to speak in open public hearing?

I don't see anybody at this time, and there's been nobody prior to this meeting that has wanted to speak in public hearing. So we will end this open public hearing.

DR. PRIOLA: Okay, thank you. With that, then, I think we can move on to the closed committee discussion, and so if the committee members would still stay on the line, on the phone, so we'll shut down the web broadcast again and move on to the closed committee discussion.

MR. EMERY: Correct. I will come back on and let you know when we have cleared the room, and when we've had the webcasting turned off.

(Whereupon, the Open Session was adjourned at 3:10 p.m.)