Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)

124th Blood Products Advisory Committee (BPAC) Meeting

OPEN SESSION

Zoom Video Conference

April 26, 2023

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

Transcript Produced By: Translation Excellence

3300 South Parker Road, Aurora, CO 80014

https://translationexcellence.com/

Participants

Chairperson	Zbigniew (Ziggy) Szczepiorkowski, M.D., PhD, F.C.A.P.	Dartmouth's Geisel School of Medicine	Lebanon, NH
Members	Mark Ballow, M.D.	Johns Hopkins All Children's Hospital	St Petersburg, FL
	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
	Nahed El Kassar, M.D., MSc-Ph.D.	Medical Officer/Program Director, Blood Epidemiology and Clinical Therapeutics Branch (BECTB)/DBDR, National Heart, Lung, and Blood Institute, NIH	Bethesda, MD
	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
	Jeremy G. Perkins, M.D. FACP, COL, US Army (ret)	Deputy Director, Murtha Cancer Center, Associate Professor of Medicine, Walter Reed National Military Medical Center	Bethesda, MD
	Richard Scanlan, M.D.	Oregon Health Sciences 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
Alternate Industry Representative	Mark Becker, M.D.	Sr. Director, Global Plasma Procurement Medical Affairs, Grifols Plasma	Los Angeles, CA

FDA Participants	Peter Marks, M.D., Ph.D.	Director, CBER, FDA	Silver Spring, MD
	Chava Kimchi-Sarfaty, Ph.D. (Presenter)	Acting Associate Director for Research, Office of Therapeutic Products, CBER, FDA	Silver Spring, MD
	Karen Elkins, Ph.D. (Presenter)	Associate Director for Science, CBER, FDA	Silver Spring, MD
	Basil Golding, M.D. (Presenter)	Acting Director Office of Plasma Protein Therapeutics Chemistry, Manufacturing, and Controls, Office of Therapeutic Products, CBER, FDA	Silver Spring, MD
Designated Federal Officer (DFO)	Christina Vert, M.S.	Division of Scientific Advisors and Consultants, CBER, FDA	Silver Spring, MD
Alternate DFO	Marie DeGregorio, B.A.	Division of Scientific Advisors and Consultants, CBER, FDA	Silver Spring, MD
Administrative Staff Director	Prabhakara Atreya, Ph.D.	Division of Scientific Advisors and Consultants, CBER, FDA	Silver Spring, MD
Committee Management Officer	Joanne Lipkind	Division of Scientific Advisors and Consultants, CBER, FDA	Silver Spring, MD

Table of Contents

Call to Order

Dr. Ziggy: Good morning, everyone. It is my pleasure to welcome everyone to the 124th meeting of Blood Product Advisory Committee. I would like to welcome all who will participate 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 the 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 Dr. Ziggy. I'm a Professor of Pathology and Laboratory Medicine and Professor of Medicine at Dartmouth Geisel School of Medicine in Hanover, New Hampshire.

As we continue our meeting 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 research programs that take place within CBER.

Specifically, we'll hear an overview of the research programs in the Division of Hemostasis, office of Plasma Protein Therapeutics Chemistry, Manufacturing, and Controls, Office of Therapeutic Products, Center for Biologics Evaluation and Research. Please note that the naming of the offices was recently changed, and our speakers will explain in greater detail these administrative changes.

FDA is tasked with regulating a wide range of different biomedical activities that are always changing and advancing, and the complement to the regulatory work that they do, various offices within CBER maintain basic and translational research programs that are meant to align with their regulatory mission. The Division of Hemostasis research program to be presented

today underwent comprehensive external review last year, including a site visit of November 3rd, 2022. At this point, I would like to hand the meeting over to Christina Vert for administrative announcements, roll call, and conflict of interest statement.

Administrative Announcements

Ms. Vert: Thank you, Dr. Ziggy. Good morning, everyone. This is Christina Vert, and it is my great honor to serve as the Designated Federal Officer, DFO, for today's 124th Blood Products Advisory Committee meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research, CBER, and the Committee, I am happy to welcome everyone for today's virtual meeting.

Today the committee will meet in open session to hear an overview of the research programs in the division of Hemostasis in the Office of Plasma Protein Therapeutics, Chemistry, Manufacturing, and Controls in the Office of Therapeutic Products, OTP, in CBER. Today's meeting and the topic were announced in the Federal Register Notice that was published on March 2nd, 2023. Can we put up the slides again? Thank you. Okay, next slide.

At this time, I would like to introduce and acknowledge outstanding leadership of my division director, Dr. Prabhakara Atreya, who will be my backup DFO, and the excellent work of my team whose contributions have been critical for preparing for today's meeting. My team includes Marie DeGregorio, Ms. Tonika Burke, Ms. Joanne Lipkind, and Ms. Lashawn Marks. I would also like to express our appreciation to our av, Leon Montgomery, Juan Silva, Oswaldo Moscoso, and Kyle Steichen in facilitating the meeting today. Also, our sincere gratitude goes to many CBER and FDA staff working very hard behind the scenes trying to ensure that today's virtual meeting will also be a successful one like all 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 Debbie Dellacroce and Catherine Diaz. Next slide.

Roll Call

Ms. Vert: We will begin today's meeting by taking a formal roll call for the committee members. When it is your turn, please turn on your video camera, unmute your phone, and then state your first and last name, organization, and expertise very briefly. When finished, you can turn your camera off so we can proceed to the next person. And please see the memo roster sides, in which we will begin with the chair, Dr. Ziggy.

Dr. Ziggy: My name is Dr. Zbigniew Szczepiorkowski. I'm present in this meeting, and I hail from New Hampshire from Dartmouth-Hitchcock Medical Center. My expertise is in transfusion medicine.

Ms. Vert: Thank you. Dr. Ballow.

Dr. Ballow: Good morning, everyone. Apparently, I don't have control over my video. Maybe AV does. Any rate, Mark Ballow, affiliated with University of South Florida. My area of interest and expertise is allergy and immunology, particularly immunology, immunoglobin replacement therapy in patients with primary antibody deficiencies.

Ms. Vert: Thank you, Dr. Basavaraju.

Dr. Basavaraju: Hi, I'm Sridhar Basavaraju. I'm the Director of the CDC Office of Blood, Organ, and Other Tissue Safety.

Ms. Vert: Thank you. Dr. Bloch.

Dr. Bloch: Hi, I am Evan Bloch. I'm the Associate Director of Transfusion Medicine at Johns Hopkins University School of Medicine.

Ms. Vert: Thank you. Next slide. Ms. Cumming.

Ms. Cumming: Good morning. Melissa Cumming, Senior Epidemiologist with the Massachusetts Department of Public Health. Expertise areas, hemovigilance and epidemiology.

Ms. Vert: Thank you. Dr. El Kassar.

Dr. El Kassar: Good morning. My name is Nahed El Kassar. I am a medical officer in the Clinical and Epidemiology Branch at the Division of Blood Diseases and Resources at the National Institute of Heart, Lung, and Blood. And my expertise is an adult hematology, transfusion medicine, and immunology.

Ms. Vert: Thank you. Ms. Lattimore.

Ms. Lattimore: Good morning. I'm Susan Lattimore. I'm the Associate Director for the Hemophilia Center at Oregon Health and Science University, and I'm here as a consumer representative.

Ms. Vert: Thank you. Dr. Maldarelli.

Dr. Maldarelli: Yes, good morning. My name is Frank Maldarelli. I'm at the National Cancer Institute, NIH, where I'm the head of the Clinical Retrovirology section. My expertise is in HIV pathogenesis and HIV and Viral Diagnostics.

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

Dr. Marques: Good morning. Can you hear me? Yes, you're fine. Okay. I'm Marissa Marques. I'm a pathologist at the University of Alabama Birmingham. My specialty is transfusion medicine.

Ms. Vert: Thank you. Dr. Perez. Dr. Perez? Okay. We'll have to come back to her. Let's see. Okay. Dr. Perkins.

Dr. Perkins: Hey there. My name's Dr. Jeremy Perkins. So I'm a clinical hematologist oncologist at Walter Reed National Military Medical Center. I'm the Department of Defense Representative on the Blood Product Advisory Committee. I focus on malignant hematology myeloma, lymphoma, leukemia. But I also have a little bit of a background in transfusion medicine as it relates to combat casualties.

Ms. Vert: Thank you, Dr. Scanlan.

Dr. Scanlan: Yeah. My name is Richard Scanlan. I'm a pathologist and Professor of Pathology and Director of Transfusion Medicine at Oregon Health Sciences University.

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

Dr. Sherman: Hi, my name is Ken Sherman. I'm a Professor of Medicine at the University of Cincinnati College of Medicine. I am a hepatologist and virologist with an interest in viral hepatitis in immunosuppressed populations. Thank you.

Ms. Vert: Thank you, Dr. Wahed. Hi, this is Abdus Wahed. I am a Professor of Biostatistics at the University of Rochester. My expertise is in biostatistics clinical trials and individualized treatment regimes.

Ms. Vert: Thank you. Dr. Becker.

Dr. Becker: Hi, good morning. My name is Dr. Mark Becker. I am the Senior Director of Global Plasma Procurement Medical Affairs for Grifols Plasma. And I am participating today as the alternate industry representative.

Ms. Vert: Thank you. And we'll go back and see Dr. Perez. Ah, yes, welcome.

Dr. Perez: I'm here. I don't know why you couldn't hear me before. Ah, good morning. I am Dr. Perez. I am an allergy immunologist. I treat children and adults with immune deficiency and my expertise of gamma globulin therapy.

Ms. Vert: Thank you. Great, thanks everyone. We have a total of 15 members, 14 voting and one non-voting member. I would now like to acknowledge CBER leadership and management, including Dr. Marks, Dr. Elkins, Dr. Golden, Dr. Kimchi-Sarfaty, and Dr. Farsheed, some of whom will be joining the meeting later today, and others who will be providing overview presentation shortly. So I'll just ask if Dr. Marks is available. Yes, please go ahead and make any remarks.

Dr. Marks: No, just want to say welcome to everyone and thank everyone for participating. Appreciate people on the West coast getting up early to do this. And this is really important for us to be able to get the type of feedback from these sessions. So thank you very much.

Ms. Vert: Thank you. Thank you very much for taking the time to join, as well. Okay. We'll go ahead and put the slides up. Yes. Before I begin reading 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 the feedback. If you have raised your hand and are called upon to speak by the chair, Dr. Ziggy, please turn on your camera, unmute, state your name, speak slowly and clearly so that your comments are accurately recorded for transcription and captioning. Thank you.

Conflict of Interest Statement

Ms. Vert: Now I will proceed with reading the FDA Conflict of Interest Disclosure Statement for the public record. Welcome to the April 26th, 2023 meeting of the Blood Products Advisory Committee. The Food and Drug Administration is convening virtually today, April 26th, 2023, for the 124th meeting of the Blood Products Advisory Committee, BPAC, under the authority of the Federal Advisory Committee Act, FACA, of 1972. Committee will meet in open

session to hear an overview of the research programs in the division of Hemostasis, Office of Plasma Protein Therapeutics, Chemistry, and Manufacturing Controls, Office of Therapeutic Products, in the Center for Biologics Evaluation and Research.

Per agency guidance, these topics are determined to be non-particular matters, which would 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 12:05 PM to 1:00 PM to permit discussions where disclosure would constitute a clearly unwarranted invasion of personal privacy, 5 U.S.C. 552b(C) (6)). Dr. Zbigniew Szczepiorkowski 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, SGEs, or regular federal government employees, RGEs, 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 appearance of financial conflicts of interest.

Dr. Mark Becker will serve as the alternate temporary industry representative for today's meeting. Dr. Becker is employed by Grifols Plasma Industry. Representatives act on behalf of all related industry and bring general industry perspective to the committee. Industry representatives are not appointed as special government employees and do not vote and do not participate in the closed sessions.

Ms. Susan Lattimore is serving as the consumer representative. She is employed by the Hemophilia Center Institute on Development and Disability. Consumer representatives are appointed special government employees and are screened 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 sessions.

FDA encourages all meaning 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 conflicts 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. I hope you can hear me better now.

Ms. Vert: Oh, if you could just still try to talk loud.

Dr. Ziggy: Okay. I'll try. My apologies. So thank you much, Christina, for the introductions. And now we're going to move to presentations. I would like to introduce our first speaker, Dr. Karen Elkins, Associate Director for Science, Office of the Director, CBER, FDA. And Dr. Elkins, please turn your camera on and unmute. The floor is yours.

Overview of CBER Research Programs — Dr. Karen Elkins

Dr. Elkins: Thank you, folks, and welcome. I'd like to, again, add my welcome to everybody here today on behalf of CBER. I'm Karen Elkins. I'm the Associate Director for Science at CBER. And I'd like to give you a brief overview of the research program as a whole to provide context for your consideration of the site visit report. And then my colleagues will add detail

about the specifics of the programs under review. As you all are probably well aware CBER regulates biological products, which has a specific definition in law. It comes down to the products assigned to us for regulatory oversight, include vaccines, allergenic products, live biotherapeutic products, a variety of cell, gene, and tissue therapy, and then the products that are most familiar to the BPAC, blood, blood components, and related diagnostic devices. And correspondingly we have a wide range of expertise that matches the needs for review of those products. We have a number of cell biologists, hematologists, microbiologists of many stripes, biochemists, molecular biologists, and epidemiologists, and statisticians, all prepared, well prepared to participate in the regulatory review.

A major part of our regulatory operations includes regulatory related research, which is in fact one of four explicit goals in our current strategic plan. And our research program is designed to address challenges in the development and the regulatory evaluation of the products that we are charged with the oversight for. So the way in which we do business includes the research program that is comprised of a series of PIs. And they provide ideas for investigative initiated research in the context of regulatory reviews. Our active research programs range from what you might describe as fairly basic questions to more targeted studies. They are all related to the regulatory products. And the purpose of the research program is to ensure an understanding of the state-of-the-art techniques that are the source of data that we see in regulatory decisions to ensure efficient, effective, and credible review, and to foster decisions based on sound science.

So our research program and our review efforts are firmly integrated. The people in our research programs are typically tasked with so-called product reviewers or chemistry, manufacturing, and control reviewers. They have responsibility for looking at the scientific rationale, any data that is provided for proof of concept in support of the product, for all of the,

everything related to the production techniques and the resulting product itself, for quality control testing, for any clinical assays that may be lab-based. And the devotion of their efforts can be up to about 50% for PI, somewhat less for more junior staff, compared to the amount of time spent on their research efforts. Our CMC reviewers operate as part of a reviewed team, which is usually comprised of a regulatory project manager that pulls it all together, a pharm tax reviewer, a clinical reviewer that is responsible for clinical trial design and resulting clinical data as it accumulates, and for the statistical status statistical reviewer, who lets us know if the numbers are valid.

So the science of that goes on within our research program furthers the development of products by addressing regulatory challenges, using our best knowledge and our best tools, discovering what we need to know to fill gaps, and using that knowledge to inform regulatory decisions and risk benefit evaluations.

You are not, but we are within a facility on Silver Spring on the White Oak Campus. We have about 450,000 square feet for about 150 labs, they range from BSL 1s to BSL 3, and corresponding offices for our research staff. We have on campus four major core facilities for flow cytometry, for imaging, for high performance computing, and for all things related to biotechnology. And we have a state-of-the-art vivarium that is well equipped with a variety of useful capabilities. Our scientists, like scientists everywhere, have active collaborations throughout the world. The majority of them are with other academic institutions and other government agencies, but we do have ways to manage collaborative interactions with our industry partners. And these are reflected in a variety of external agreements, everything from simple material transfer agreements through formal creatives and external grant programs.

We think that doing business this way has a number of benefits. It inherently prepares us for future innovative products and for public health challenges. We have been living the reality of a public health challenge for the last three years, obviously. And I think the value of having practicing scientists on the ground ready to go has been well demonstrated during the pandemic. Our research program develops data and tools that directly support the development of a plethora of products, and we seek to fill any knowledge gaps that may advance product development, including knowledge that informs policy development and our regulatory decision making. Another important aspect not to be overlooked is that having the research program definitely facilitates recruitment and retention of highly trained scientists that have the expertise in hand to efficiently and effectively review our regulatory submissions.

So our research program is evaluated in a variety of ways, and this gets to the topic of today's meeting. We have an annual project review system, in which people write reports, and those were reviewed and discussed at all layers of management. We have a formal horizon scanning program that is conducted periodically, typically about every four years. New projects receive special attention and are reviewed as they come online before they go too far.

And then we have an external site visit program that is today's subject. Site visits are comprised of a committee of external impartial experts who virtually review our program. They receive an extensive report of activities in the research program for about the last four years. The timeframe for those has slipped during the pandemic, and it's been more like five years. They comment on the report. They join us for a virtual day of meetings in which investigators provide formal presentations and investigators are interviewed by committee members. And then all of that information is used to create the site visit committee's report of their findings with recommendations for about how progress has been made and the comments on future activities.

So we evaluate our, other criteria for evaluation of our research will be familiar to you. They include obviously dissemination. We expect people to publish, to present, to, when applicable, turn their discoveries into technology transfer activity as needed. We expect it to be relevant to our mission, to align with our goals and objectives, and to inform our review capabilities. We expect it to have impact. We expect to see evidence that our research activities are being taken up by the scientific community and are aiding and abetting all of our regulated stakeholders. And some things do have a particular regulatory focus, developments of reference standards, for instance. We don't expect our advisory committees to be heavily involved in that evaluation, but we do obviously keep track of that internally.

So the site visit report has been drafted by the committee that reviewed the unit in question today. That was chaired by two members of BPAC, and they will be discussing this as things go along. That draft report has been hopefully distributed to you all. And so three things can result from today's meeting. You may choose to accept the report. You may choose to amend the report. Or you may choose to reject the report and send it back to the site visit team for further action.

Whenever the final report is approved by the full advisory committee, it is used in lots of ways. Obviously, it goes to the PI, then they take all of the input under advisement to improve and refine their research program. All of the supervisors and associated managers scrutinize it and discuss internally the program's progress and expectations for the next upcoming review period. And the report may impact resource allocations, of course subject to resource availability.

So I want to thank you all very much for your input into this process. It's absolutely critical to ensure that we maintain high quality research programs and that those in turn

contribute to fulfilling our regulatory missions. So we are very grateful for everyone's service and critical input and critique of our research programs. And I'm happy to answer any questions.

Q & A

Dr. Ziggy: Dr. Elkins, thank you for excellent presentation. I hope you can hear me better now.

Dr. Elkins: Ah, yes. Mm-hmm.

Dr. Ziggy: Okay. Thank you so much. And I would like to open the presentation to any questions from the committee members. Please raise your hand, and when called, turn your camera and unmute your microphone prior to asking your question.

Dr. Elkins: And of course, I and my colleagues are available to you all day as questions arise during the course of the proceedings.

Dr. Ziggy: Great. I don't see any questions, however I may ask one. And here's the following. Obviously as you mentioned, there is a significant impact of pandemic on the research and availability of laboratories to ask. And I think we've seen in the report a very ingenious ways of actually dealing with this problem. Can you comment to us what other mitigation strategies your office considers to increase the research access of FDA? What other options you thought about that, what things might be good?

Dr. Elkins: Well, I think your question is asking about future activities, but I can comment probably better on what happened during the pandemic, and we will continually learn lessons from that. FDA as an organization and the federal government as an entity you know, started the pandemic by imposing severe occupancy restrictions. And that, you know, we, like the rest of the world, shut down. We came back very slowly. We had several research programs that started up Covid-related activities, and those were allowed to continue. The non-Covid related activities

that had involved critical material, ongoing animal experiments, for example, also continued, at least to the point of rendering them safe and generating useful data rather than wasting materials.

But we had to be honest, a good year's worth of very slow activity. And that, in turn, did impact the progress at the bench. We had a slow ramp up after, I would say, the first year, as well. All throughout that, and continuing now, which we are now dealing with the reality of a hybrid work environment, and particularly a hybrid and largely remote environment for our regulatory reviewers. We have tried to support people and their research activity in terms of giving them the tools to interact remotely, in terms of making material accessible and securing materials in animals as best we can.

It has been a challenge, I have to admit, and it continues to be a challenge. I think it's had an impact on our scientific climate, like here, like it has everywhere. And the remote work, the hybrid work environment, is a particular feature of that. We have some activities coming up in which we will have what I hope are fairly frank discussions among all of the researchers about how they view operating a lab and a hybrid environment. Nobody has an incubator in their garage. So this is going to be an ongoing challenge and we recognize that. I hope that helps.

Dr. Ziggy: Yeah, absolutely. Thank you so very much. Are there any questions from the committee? Any additional questions?

Dr. Elkins: I feel obliged to comment also, particularly during the early days of the pandemic, but continuing on that experience now, I think people were incredibly creative about how to use their time well. You know, a lot of bioinformatics analyses happen that might not have had the level of detail that they would have otherwise in the early days. A lot of review papers got written. You know, keeping the trainees well trained and trying to create a good experience from

them was really a difficult challenge. And the silver lining of that is that all of the lessons learned about how to shift will still continue to stand us in good stead going forward, I think.

Dr. Ziggy: Great. Well, thank you very much. I think it's recognized by the committee how much hard work went over the last number of years, especially the pandemic around.

Dr. Elkins: Well, the other reality of it, maybe not so much for this particular group, but for many groups, is that they were consumed by regulatory activities. The vaccines and the platform products people particularly had a tremendous regulatory workload that made worrying about progress on the labs a little bit secondary.

Dr. Ziggy: Thank you, Dr. Elkins. Again for the committee, any other questions?

Nothing again. And we're going to move to the next presenter. And I have pleasure to introduce Dr. Basil Golding, who is Acting Director of Office of Plasma Protein Therapeutics Chemistry, Manufacturing, and Controls, Office of Therapeutic Products, CBER, FDA. Dr. Golding, please turn your camera on and unmute. The floor is yours.

Overview of OTP and Office of Plasma Protein Therapeutics Chemistry, Manufacturing, and Controls Research Programs — Dr. Basil Golding

Dr. Golding: Okay, so, welcome and good morning. I'm Basil Golding, the Acting Director of the Office of Plasma Protein Therapeutics. And we had this morning to talk about the Hemostasis Branch site visit. But before I start, I do also want to thank the administrative group, Christina, Prabha, and her group, and the audiovisual group for putting this together in a very efficient way. And particularly I want to thank the site visiting group that came in November and the advisory committee today talking about our site visit and giving feedback. It's very important. This activity is very important to maintain for us to maintain a high quality of research.

So my task today is to give an overview of the newly formed Office of Therapeutic Products and also to talk about the Office of Plasma Protein Therapeutics, which is my office underneath this so-called Super Office. So the Office of Therapeutic Products is now named as a super office, and our office of Plasma Protein Therapeutics is underneath that umbrella. So first of all, I'm going to be talking about the so-called Super Office of Therapeutic Products, OTP. And I'm looking for a laser pointer. Okay, so next slide.

So this was the old organization, and when the site visit took place in November of last year, this was the organization at the time. The office was called The Office of Tissues and Advanced Therapies. I'm not going to go through the whole organization of this office, but just to highlight so you can see the changes, when you site visited in November, we were the Division of Plasma Protein Therapeutics, and we had two branches. What I'm going to show you on the next slide is that the division was elevated to become an office. So it's now the Office of Plasma Protein Therapeutics, and the Hemostasis Branch where you site visited has now become a division with two branches. And the other branch, the Plasma Derivatives Branch has also become a division with two branches.

So this is the new organization. Again, I'm not going to have time to go through it in any kind of detail, but it's now, this is the Super Office of Therapeutic Products. So the divisions that you saw before have become offices, including our division became the Office of Plasma Protein Therapeutics. And what was a branch of Hemostasis is now the Division of Hemostasis with two branches. So the PIs, the principal investigators that you site visited are on these two branches, split between these two branches.

Okay, so what is regulated in the Super Office of Therapeutics? I'm not talking about my particular office at this time. I'll come to that later. So what's regulated are stem cells and stem

cell derived products, terminally differentiated cell therapies, therapeutic vaccines, gene therapies, xenotransplantation products, tissues and tissue-based products, and some devices and combination products.

So this is just to give you a sense of the number of submissions that we see. These are investigational new drugs, or INDs. So this is over a period from 1963 to 2021. And you can see in the later period, in the last 10, 15 years, you've seen an exponential growth of INDs in this area. And I don't have 2022, but there were over 600 submissions in 2022. So this exponential growth means obviously an increased workload, and part of the reason for the reorganization is a substantial increase in workload over the recent years. So by expanding the divisions to offices, it allows for more hiring and expanding the organization so it can deal with the workload.

Okay, so just to give you a sense of the critical activities, these are BLAs that were approved in between 2020 and 2022. So this is SEVENFACT. This is a factor VIIA approved in my division and now my office. And these are different CART T-cells approved in this office. TECARTUS and BREYANZI are both against CD-19 on B-cells, so for B-cell malignancies. And this is for multiple myeloma, a CAR T-cell that targets B-cell maturation antigen. And this product, STRATAGRAFT, is an allogeneic cultured keratinocytes for the treatment of thermal burns. And RYPLAZIM is a plasminogen, which is a human plasma derived plasminogen to treat plasminogen deficiency, approved in my division. RETHYMIC is used for immune reconstitution of the thymus in patients with congenital athymia. CARVYKTI is for treatment of adult patients with multiple myelomas, a CAR T-cell. He has another CAR T-cell, sorry, this is a gene therapy for beta thalassemia. And SKYSONA is for progression of neurologic dysfunction in children with active cerebral adrenal leukodystrophy. And Etranacogene is used for hemophilia B as gene therapy for hemophilia B factor IX deficiency.

So that just gives you some sense of the regulatory load. And in terms of the science, the office, the super office now has 17 laboratories. There were 28 publications. This is excluding my office. 28 publications in this time period. 36 external conference presentations, and seven COVID-related research products. Projects, I should say.

Okay, so now I'm turning to my office, the Office of Plasma Protein Therapeutics. So this is the organization. Myself as the acting director, Mahmood Farshid as the Acting Deputy Director. And we now have two divisions, Division of Hemostasis under Dr. Zuben Sauna, and Division of Plasma Derivatives, Acting Division Director's Dorothy Scott. And the PIs in the division of Hemostasis that you site visited are listed here. Their research will be described in a little bit more detail later on. And these are the PIs in the Division of Plasma Derivatives. And Dr. Kimchi-Sarfaty is the Acting Associate Director for Research for the whole super office, but also for our office. And Trevor Pendley is a program analyst, and Esther Sahntillaire is the program support provider.

So what do we regulate and what are our regulatory functions? So we evaluate manufacturing or CMC. We also do surveillance for adverse effects, events, I should say, and for deviation reports. We are active in policy and guidance documents preparation and review. We have members involved in harmonization. This is global harmonization involving also the Europeans and the Canadian authorities. We're involved in liaison meetings with industry. Communications to stakeholders. We set up workshops. We recently had our workshops on IGIV sensitivity reactions. We participate in scientific committees, and we answer any citizen petitions.

So these are some of the committees and working groups that we are involved with. The NIBSC, National Institute of Biological Standards in the UK. We work with the WHO. EDQM,

which is European Pharmacopoeia. We obviously work with committees that are internal to CBER and CDER and other FDA components. Multiple USP committees and working groups, and multiple industry educational groups such as PDA, CASSS, and DIA.

So how does the regulatory process work? Well, the decisions are based on scientific data showing safety, efficacy, and purity, and the decision-making process involves internal review of submissions, and if needed, presentations to advisory committees, and multiple meetings with manufacturers. The formal meetings include pre-IND/pre-IDE, IND meetings, pre-BLA, and mid and late cycle meetings during the course of BLA review.

So in terms of the actual products themselves, we have general immune globulins, specific immune globulins enriched for particular antibody specificities against infectious agents and toxins, and enzyme inhibitors that are also plasma derived for hereditary deficiencies of those enzymes such as C1 esterase and C1 proteinase inhibitor. So in the Division of Hemostasis, we regulate coagulation factors, anticoagulants, bypassing agents, hemostatic agents, and reversal agents for anticoagulants which can be associated with bleeding.

So just to give you some idea of the, our workload, so this is the last few years, you know, obviously 2023, we've just started. So we do have a large number of IND submissions. Most of them are amendments. We have over a hundred products and multiple INDs that are ongoing. And the original INDs, we see about two per month. So that would make about 10 to 20 per year. If you look at the actual BLA submissions that we received, because we have so many products, over a hundred, most of the submissions are at the bottom of these bars as the supplements, and then you have the annual reports and post-marketing submissions, and then original BLAs, which are usually the highest workload type of submission because of the volume of the submission and the importance of the submission.

So what is the scope of the research? In our office, we study the mechanisms of blood coagulation, and we look at clearance pathways for factor VIII and characterization of product related impurities in recombinant factor VIII. Assay and standard development is very critical and it involves collaboration with WHO and NIBSC. We look at immunogenicity,. It's a very important aspect of protein therapy that you can get anti-drug antibodies. So we've been looking at FC fusion proteins, factor VIIA, and also looking at immunogenicity against CRISPR/Cas9. Many people have antibodies that up against Cas9. We look at pharmacogenomic and codon automation studies of proteins. Research into aggregates in protein products. We have projects in involved with regarding counter-terrorism and pandemics, and there were several projects during Covid and quite a few publications related to COVID-19. And we also look at the efficacy of immune globulin products for different diseases, flu, Ebola, Zika, HCV, and SARS-CoV-2.

So just to give you a flavor of the output, you see 26 publications, 57 presentations in this period, well, until April 2023. It was updated. And the publication topics include this list. I don't have time to go into detail. We publish in high impact journals, and presentations are in national and international meetings. And these are some of the presentation topics.

So looking ahead, we've identified and have plans to address the following gaps in regulatory research. Bioinformatic approaches to examine immunogenicity and introducing DNA sequence changes for optimizing product yield. Looking at next generation immune globulin such as recombinant polyclonal immune globulin, modified immunoglobulins, particularly post translational glycosylation, and novel immunoglobulins against emerging pathogens and toxins. And lastly, safety issues related to platform technologies for protein modifications such as FC and albumin fusion and pegylated proteins.

So I just want to acknowledge people that helped me put this talk together, Dr. Kimchi, Dr. McElwain and Trevor Pendley. And some of the slides I borrowed from upper management and OPPT staff. So thank you for your attention and I'll be very happy to answer any questions.

Q & A

Dr. Ziggy: Thank you, Dr. Golding, for your presentation. Very, very informative. I would open the presentation to any questions from the committee members, and please raise hand if that question. Okay. Dr. Sridhar Basavaraju, can you unmute yourself? Okay. Excellent.

Dr. Basavaraju: Hi. Hi, Dr. Golding. Thanks for your talk. What's the status of the immunoglobulin therapy development for, I saw, you know, there was a bullet that you had on immunoglobulin development for Ebola, SARS-CoV-2, things like that. And I'm curious to see if you had any thoughts on how far any of those potential treatment modalities have come. And then also, I guess, with the availability of actually antivirals, is there really any role for those anymore as therapeutics?

Dr. Golding: Okay, well you, you may know, starting from the back end of your question, so there are antibodies that are approved for viral diseases. So one of the big success stories was with the antibody, again, hepatitis B. So you probably know that mothers that are positive at the time of birth, that children are given both the vaccine and the antibody. In addition to that, transplant patients, people who have chronic HPV develop hepatocellular carcinoma or hepatic failure and need a liver transplant. Without antibody to Hepatitis B, those transplants almost universally failed after a few months. But with the advent of the antibody, there was great success in keeping those livers functional and preventing recurrence of Hepatitis B.

But in general, what I would tell you regarding viral and in other infectious diseases, antibodies are great in preventing disease. So another success story is antibodies against hepatitis

A. So you know, when there are outbreaks, post-exposure prophylaxis is very successful in preventing spread of Hepatitis A. And when it comes to actual treatment of disease, the success is much more limited. And we actually published a paper during the pandemic which addressed this problem. And we think that part of the problem is due to the viral or infectious disease load. So if you focus on Covid, for example, if you wait until the patients are hospitalized and have a high viral load, the experience was, you know, several trials were performed. The experience was that the antibodies didn't work. Monoclonal and polyclonal were not very effective. But if you managed to get the patients very early in the disease, when the viral loads are relatively small or low, the antibodies have a chance to work, and there was greater success.

And I think it's simply because if you have immune complexes, antibody plus virus, the antibody gets cleared very quickly. Unless you have antibody access, which requires daily or frequent high dose antibody, you're not going to have success in patients who have a high viral load. So I think that is the, you know, I could go on. I'm sorry. This is a major interest of mine. I don't want to take up all the time. Say, if that satisfies you, I will stop.

Dr. Basavaraju: It does. I was curious, like for some of the other, because I know that in the setting of SARS-CoV-2 for example, some of these antibodies worked for a little while and they stopped working based on the development of variants.

Dr. Golding: Oh wow. Yes. That's another issue here. Yeah.

Dr. Basavaraju: Yeah. So then what is the status with like some of the other diseases like Ebola, some of the ones that I haven't followed as closely. I think you had Zika and Ebola and things like that, on that.

Dr. Golding: Okay. So again, what you mentioned is obviously a major challenge for Covid and other viruses that can mutate frequently. But if you have viruses that mutate frequently,

keeping up with the, you are always, the virus seems to be able to mutate more quickly than we can make antibodies against the virus. So that is a major issue. But for the other diseases that you mentioned, Ebola, Zika, and so on. You know, those were issues several years ago for the Agency and for public health. They do not tie on the listed right now, but the history was that monoclonals were made, polyclonals were made, and there was some success with polyclonals in Ebola, for example, but that required cocktails and also required treatment early in the disease. So there was some success with that.

With Zika, there was some success with Zika. We didn't get to the point where any of the products were approved. We did develop in-house all kinds of assays to measure antibodies and antibody neutralization. So part of it, our active, whenever something like this emerges, a new disease emerges, at the FDA, you know, different parts of the FDA are doing different things, but one of the important things that we do is try and establish assays to see if we can measure neutralization. So establishing vitro techniques that correlate with the possible efficacy. But, you know, your question, it's a huge challenge when it comes to viruses that that mutate, yes.

Dr. Basavaraju: Thanks.

Dr. Maldarelli:This is Frank Maldarelli. Just to follow on to that a short question, and does the FDA have a position for the utility of these monoclonals or polyclonals in situations of severe disease, you know, individuals who are in ICUs and so forth, where, you know, there may be a need for something in addition to antivirals in a very extreme circumstance.

Dr. Golding: Well, as I pointed out, unfortunately, when patients are in, by the time they're in an ICU, the, you know, the viral loads are usually so high that it's very difficult for antibodies to overcome that viral load. There hasn't been good success in those situations. The success is in prevention or early treatment. And once you, at that point, my understanding even, you know, I

don't regulate monoclonals, but from the literature, the monoclonals were also largely ineffective at that, at that point. So unfortunately, when you get to that point, the antibodies are not going to be very helpful. There is some evidence that polyclonal immune globulin and, you know, the regular IVIG has been used for many autoimmune diseases successfully, and it has some anti-inflammatory effect. And it's not really well understood what the mechanism is. So people have used intravenous immune globulin for very severely ill patients with, I would say, a modicum of success, probably because of some kind of anti-inflammatory action, we were not well understood.

Dr. Ziggy: Thank you, Dr. Golding. We have a question from Dr. Kassar.

Dr. Kassar: Yes. Thank you. Thank you, Dr. Golding, for your talk. That's very informative. My question is about the antibodies to CRISPR and Cas9. So at HLBI, as you know, we're very interested in gene therapy using this technology in patients with sickle cell disease. So how concerned should we be about those antibodies?

Dr. Golding: Well, it turns out, you know, this is work done by Dr. Zuben Sauna and published. But it works out that a high percentage of people in the community at large, in healthy individuals, have low titer antibodies against Cas9, which is not surprising, since the Cas9 is derived from bacteria that are present in and can infect people. So the antibodies, obviously, if you introduce CRISPR therapy and you have Cas9 being presented by the cells that I've been introducing to the patient, the antibodies could interact with the Cas9, form immune complexes, and if the Cas9's expressed on the surface of the gene expressing cells, it could interfere with, it could cause damage to the cells, even kill our cells by IDCC or other mechanisms.

But I, you know, I think what is more important than the antibodies is the T-cell. You know, when you have antibodies, in most cases you need help with T-cells. And the help with T-

cells can also induce CD8 cells, which are cytotoxic cells. So in addition to, the antibody isn't easy to measure and it's relatively, and in this case it would be indirect. In other words, what I'm trying to say, having the antibody in a patient implies that they have helper T-cells. And if you introduce Cas9 construct and the Cas9 expressed on the surface of cells, the T helper cells may help CD8 positive T-cells to kill the gene expression cells, which is counterproductive. Right? So I think there should be a move towards modifying the Cas9. So in by engineering to remove the epitopes that are immunogenic or finding another way of doing editing without use of something like Cas9 that can be immunogenic.

Dr. Kassar: Thank you.

Dr. Ziggy: Thank you again. And that was the last question. Thank you, Dr. Golding, for responding to the questions. And thank you committee members for asking them. I would like to move to the next presentation and introduce, next speaker is Dr. Chava Kimchi-Sarfaty, who is the Acting Associate Director for Research, Office of Therapeutic Products at CBER FDA. Dr. Sarfaty, please turn your camera on and unmute. The floor Is yours. Thank you.

Overview of Division of Hemostasis Research Programs — Dr. Chava Kimchi-Sarfaty

Dr. Kimchi-Sarfaty: Thank you very much. Okay. My name is Chava Kimchi-Sarfaty, and currently I'm the Acting Associate Director for Research of the Super Office. I'm going today to discuss the Hemostasis research program and to tell you more about each of the four programs that were site visited. Before I go further, I would like to show you the current new organization of the Office of Therapeutic Products and specifically the four PIs that were under the site visit review. So, as Dr. Golding mentioned, we are part of the Office of Plasma Protein Therapeutics. Now, the four of us are under the Division of Hemostasis that is led by Dr. Zuben Sauna. And currently now there are two branches. In the past and during the site visit, Dr. Tim Lee led the

branch and the FFA reported to him. And now there are two branches. One is led by Alexy Khrenov, and under him are Zuben Sauna and myself. And the second branch is led by Dr. Mikhail Ovanesov. He's the branch chief, and he and Dr. Andrey Sarafanov are in this branch.

So from here I can move to start to discuss the first program by Zuben Sauna. And this is regarding the immunogenicity of protein-based therapeutics. So there are three major goals to Sauna's project. One is regarding the immunogenicity of proteins used in therapeutic application. And the goal of Dr. Sauna's lab is to identify the genetic and phenotypic determinants of immune responses to therapeutic proteins and elucidate the molecular mechanisms of immune responses. The second goal is to improve therapeutic outcomes, and specifically the group is focusing on minimal immunogenicity. And the third goal of this group is regarding computational and biophysical studies related to SARS-CoV-2 virus. Here, the group aimed to use bioinformatics tools to understand the diverse clinical symptoms and pathologies reported in COVID-19 patients, and to design novel antibody and non-antibody-based SARS-CoV-2 binding reagents.

So what did Sauna's group achieve since 2017? And I mentioned 2017 because before last November 2022 this was the site visit. So they have used statistical methods and AI-based tool to identify variables associated with risk of developing anti-drug antibodies to Factor VIII used to treat hemophilia A. They developed approaches for assessing the immunogenicity risk of Cas proteins used in gene editing. They designed and evaluated Factor Xa variants that could successfully reverse uncontrolled bleeding following the use of Direct Oral Anti-Coagulant apixaban. And they developed a workflow to design antibodies that bind specifically to multiple SARS-CoV-2 variants with nanomolar binding affinity. All the work is mission relevant, and we regulate in our office these products.

They have published since 2017 32 publications. Four of them were published since the last site visits. Well, what were the accomplishments since the last site visit in November, 2022? Zuben's group initiated work on addressing the question: how do different population cluster with respect to HLA, and how could in this impact immunogenicity between populations? They initiated work on comparing immunogenicity of Cas from different organisms. They initiated studies on safety of reversal agents. They design less immunogenicity variants of Cas9 with respect to engagement of HLA Class I molecules, and this is an ongoing project. They initiated studies on evaluating the neutralization of antibodies that targets SARS-CoV-2 virus. They initiated studies on evaluating next generation SARS-CoV-2 binding agents, and these are the Ankyrons. And as I mentioned earlier, six manuscripts were submitted for publications; four were accepted.

The next program, which I'm going to describe is led by Dr. Mikhail Ovanesov. And this is regarding study of the regulation of blood coagulation by coagulation Factors VIIa, IX, and XIa. The group in general is looking at drug development and control of drug quality that require better and more predictive and accurate hemostasis assays. The Ovanesov laboratory collaborates on assay harmonization and reference standards, and they refine new and existing hemostasis assay by evaluating the assay limitations and comparing the assay results with evidence of safety and efficacy in animal models.

The goals of the research programs, there are two goals that are very related to each other. The first one is to develop analytical methods that can mitigate the risks of bleeding and thrombosis in patients treated with plasma protein products, which we regulate in our office. They develop method modifications to measure hemostatic and thrombotic activity more accurately or with better sensitivity, and they aim to connect evidence of assays' predictive value

with the mechanism of drug action and thrombogenicity. The second goal of Ovanesov's program is to develop international standards for coagulation factors. And here the laboratory participates in collaborative studies to develop harmonized methods and international standards for coagulation factors.

Since 2017, the group had 18 peer review publications, two of them since the last site visit. And these were regarding thrombin generation assay viability and standardization, Factory XIa Thrombogenicity, and mouse pharmacokinetics and tail bleeding studies. The group was part of many public meetings and workshop regarding hemophilia therapeutics, and one example is the WHO hearing on development of product-specific reference material for Factor VIII and Factor IX products that happened in 2019.

The group carries 12 collaborative lab studies. Two of them are since the last site visit, and these are regarding international reference standards and assay studies. And I will give you two examples. One of them is the WHO Third International Standards for von Willebrand Factor Plasma. They have used three methods here. And another example is the WHO third international standard for thrombin. Again, they have used three different methods in the collaborative study.

The next program I'm going to describe is by Andrey Sarafanov. And this program is towards longer acting Factor VIII products with higher purity. Dr. Sarafanov's laboratory seeks to facilitate development of longer-acting, extended plasma half-life therapeutical Factor VIII products. All the aims of this lab is regarding Factor VIII and to understand structurally compromised Factor VIII protein in approved products as an impurity and facilitate the control of these impurities. Basically, they're using four different systems. They're using purified material, cell culture, animal models, and in silico modeling.

The two main goals of Sarafanov's laboratory is to elucidate mechanisms of Factor VIII clearance from circulation. Mainly the focusing on lOP, they aim to characterize the mechanism of Factor VIII interactions with plasma clearance receptors, to generate modern Factor VIII fusion proteins that have extended plasma half-life, and to elucidate the reasons for Factor VIII activity assay discrepancy in Hemophilia A patients subjected to gene therapy. The second major goal for this program is to characterize structurally compromised protein in Factor VIII products. Here they aim to characterize the Factor VIII subpopulation that is are unable to bind VWF, von Willebrand brand Factor, in recombinant Factor VIII products, to characterize Factor VIII tyrosine sulfation as a factor affecting safety and efficacy of recombinant Factor VIII products, and they are quite advanced in this aim and to develop the analytical method to address these questions.

The major scientific accomplishment since 2017 were to elucidate the mechanism of Factor VIII interaction with its major clearance receptor in plasma, the hepatic LRP, to develop a method to analyze the VWF non-binding protein in recombinant Factor VIII products, characterized all the US recombinant Factor VIII products for the content of this impurity, and characterized the structured properties of this protein. They accomplished the characterization of tyrosine sulfation in all US recombinant Factor VIII products. And this was finalized, or almost finalized, since the last site visit. And they published on all these four papers and presented in 19 research conferences, including the ISTH.

The last program is my program, and this is regarding the synonymous variations in health and disease. And we have three major goals of our research programs. The major project is regarding the impact of genetic variant on therapeutic proteins, and these are recombinant proteins and gene therapy. We aim to investigate the impact of synonymous variants on the

biological and chemical properties of therapeutic proteins and establish AI tools to predict the performance of genetically engineered therapeutics. Another goal of our research program is regarding ADAMTS13 in health and disease. Here we aim to explore methods for assessing ADAMTS13 activity and investigate the role of ADAMTS13 and VWF factor in unique patient populations in health and disease, such as the sickle cell disease. And the third aim is regarding SARS-CoV-2 genetic characteristics and interactions with coagulation proteins. Here we aim to evaluate the nucleotide composition, codon usage, and mutational properties of SARS-CoV-2 and identify host-viral protein complexes between coagulation-related and SARS-CoV-2 proteins.

What were the major scientific accomplishments since 2017? We published 18 peer reviewed publications and one book, which I co-edit. And here, regarding the impact of genetic variants in therapeutic proteins, we identified novel examples, how synonymous variants and codon optimization can impact mRNA and protein properties in multiple different models. We are using item ADAMTS13 Factor IX as models. These are products that we regulate, and we established codon usage resources for their evaluation. This is publicly available. Regarding ADAMTS13 in health and disease, we published eight peer review papers, and we have one patent application. Here we elucidated the role of van Willebrand Factor ADAMTS13 in many clinical conditions, including its role in preoperative thrombosis, COVID-19 associated bleeding disorder, sickle cell disease, and in patients with severe congenital heart disease. And regarding SARS-CoV-2, we published five peer reviewed articles. We identified promising sites within the nucleocapsid and spike proteins for deoptimization and vaccine development. We established a pipeline for identifying coagulation-related host viral-protein complexes and more. All of this is in silico work. Of course, we participated in many internal and external conferences.

Since November of 2022, we initiated pharmacological and immunogenicity studies on codon and codon-pair optimized ADAMTS13 and Factor VIII and the implication. And we are looking at the implication of lentiviral and AAV, adeno-associated virus, delivery. We are developing a tRNA bioinformatics pipeline and synonymous variant prediction tool. There are ongoing projects on investigating ADAMTS13-independent form VWF regulation in other diseases. And we are performing a meta-analysis on relationships between endothelial disfunction, coagulation, and SARS-CoV-2 infection. Two manuscripts were accepted, and two manuscripts are under review.

I would like to conclude and tell you generally about the four programs. And before that, I would like to thank really our management for the continuous support that we get. So OPPT have established four productive programs in the Hemostasis Research Program with strong track record of publications. The research from the program has been presented in many conferences. As you saw, our programs have initiated numerous emergency SARS-CoV-2 projects in response to the public health crisis. Again, as I mentioned. And our programs have characterized numerous biological products and developed novel assays for their assessment to enhance FDA regulation. Thank you. I will entertain any questions now. Thank you.

Q & A

Dr. Ziggy: Thank you Dr. Kimchi-Sarfaty. I think it was a wonderful presentation. Again, I congratulate your laboratories on this tremendous amount of work done over the last several years. So I would like to open this presentation to any questions from the committee members at this point. So please raise your hand, and when called, turn on camera and unmute your microphone prior to asking a question. I see, yes, Dr. Kassar please.

Dr. Kassar: Yeah. Thank you very much. That's very exciting. Again, I'm interested in your work on ADAMTS13 and von Willebrand. Is it possible that you summarize what you know on sickle cell disease and pregnancy, for example? Because I'm just doing a workshop in May on sickle cell disease and reproductive health.

Dr. Kimchi-Sarfaty: Oh, wow. So actually we did not focus on pregnancy with regarding ADAMTS13 von Willebrand. And this is a very interesting topic. And we would like to expand it. I mentioned that we would like to expand it in other different situations. We did quite a lot of work and published regarding the sickle cell, and here there were contradictory evidence in the literature about different assays and the level of ADAMTS13 as a result in sickle cell disease patients. It seems to be that each group was using a different assay, and some of them reported about very similar normal levels of a t sine in sickle cell disease patients even during crisis. And some of them reported about lower ADAMTS13 and higher von Willebrand Factor. What we did is we used all the methods for ADAMTS13 study and expression and activity, and we looked at discrepancy between the methods for this specific population, and also concluded that, specifically in sickle cell disease patients, there are other proteases that cleave von Willebrand Factor. And these proteases, probably under hypoxia condition that is probably a crisis situation in sickle cell, they're elevated. So they're not sufficient really to get rid of very high molecular weight of von Willebrand Factor. But they are contributing to the proteolysis of von Willebrand factor.

So it's interesting to understand really that different methods are revealing in different populations different results. And we need to be very careful when we are looking at those methods. And already others have published about hemolytic samples, about bilirubin and

samples that contain high bilirubin, and so on. So this is additional layer of ADAMTS13 methods discrepancy.

Dr. Kassar: Thank you.

Dr. Ziggy: Thank you very much. I recognize two committee members, and those will be the last two questions before the break. So Frank Maldarelli, please. Dr. Maldarelli.

Dr. Maldarelli:Yes, thank you for the great presentation. My question was regarding, you refer to artificial intelligence programs that you're employing. And I'm curious whether these will include things like new language processing models that are used to depict the three-dimensional structures of proteins or changes in sequences and whether those AI processes themselves would be subject to regulation.

Dr. Kimchi-Sarfaty: That's very interesting. So currently we are working only on the research arena about this AI. Certainly this adds a lot of knowledge to our reviewers. One of the AI applications is a predictive tool that we already developed about co-occurring mutations. As you know, there are thousands of different predictive tools that are looking at recombinant protein or gene therapy sequences, but they can examine one mutation at a time. And we have looked at the core carrying mutation using AI tools.

The other thing that we are looking now at predictive tool for synonymous mutation. And here, the 3D is really important because there are development of 3D tools to look at effects of synonymous mutations that in the past nobody believed that can change actually the 3D structure of proteins. And now the tools are included in our predictive tool that we are developing. I hope I answered some of your question.

Dr. Maldarelli:Yes, thank you. That's very helpful. I just note that some of the language processing models are being developed by very computationally intensive groups such as Google

and Meta. And so they may actually be a part of, I wonder whether they'll become part of your portfolio to oversee.

Dr. Kimchi-Sarfaty: Right. So some of our products are reviewed also by computational experts, and I should mention that at CBER, we have established a very strong group called Hive that is only computational experts that are helping both the regulators and the researchers in their projects. This is a very nice collaborative between the biologists and in silico computational work. And they are really trying to understand and to learn what is now open and available to the public to try to bring it to CBER and to also educate all the scientists in the new tools. So that hopefully answers.

Dr. Maldarelli:Yes. Thank you. It's very forward looking of you.

Dr. Ziggy: Thank you so much. And we have one more question from Dr. Marques, and I just want to look at a time and say that may be a very short answer, please.

Dr. Marques: Yes. Hi. Good morning. Thank you so much for your presentation. So many interesting projects. I wonder if you'll be willing to elaborate or to propose which one is more likely to change clinical practice first. Well, which one do you think will come to the forefront of our lives in the near future?

Dr. Kimchi-Sarfaty: Okay. Thank you for asking this question. I believe that what we are trying to do in CBER, and I think we are quite successful, that all our programs are mission relevant, and all our program are looking at the horizon and trying to really understand what are we expecting in the future. And we are integrating this into our programs. We are not maintaining projects regarding either products or concepts that are no longer part of the mission of our office or CBER. And therefore I believe that really all the four programs are highly relevant to what we are expecting in the future.

Dr. Marques: Thank you.

Dr. Ziggy: Thank you so much. Thank you for the questions and, again, wonderful presentations from all speakers and presenters. I would like to now dismiss the committee for actually only five minutes till 11:05 Eastern Daylight Time, and at which we continue our meeting. So thank you so very much everyone, and have a five-minute break.

Open Public Hearing

Dr. Ziggy: Okay. It is 12:06 or so. And this is this part of the meeting where we have open public hearing. However, I was informed that there were no formal oral requests being received by the deadline, and therefore we will conclude the open session at this point, because no hearing will be presented. And only members and FDA leadership should stay connected. So thank you very much. Thank you for those who attended, and wish you a very good day.