Food and Drug Administration

Center for Biologics Evaluation and Assessment

113th Meeting of the

Blood Products Advisory Committee

June 20, 2016

FDA White Oak Campus
Building 31, Great Room
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P R O C E E D I N G S (8:30 a.m.)

Agenda Item: Call to Order and Opening Remarks

Susan Leitman, M.D., Acting Chair, BPAC

DR. LEITMAN: Hello to all the committee members of the Blood Products Advisory Committee. This is Dr. Susan Leitman speaking. I am the acting chair for this BPAC meeting in the absence of the usual chair, Dr. Chris Stowell.

I am calling to order the 113th meeting of the Blood Products Advisory Committee. I would like to introduce the committee members of BPAC who are participating on this phone call. I'm going to read them alphabetically and after I state your name, could you tell us who you are and give us a little introduction to yourself? I will start with Dr. Basavaraju.

DR. BASAVARAJU: Hi, I am here. I'm a medical officer with the CDC office of blood, organ, and other tissue safety.

DR. CHITLUR: Hi, I'm Meera Chitlur. I'm a pediatric hematologist at the Children's Hospital of Michigan and the director of the HTC here.

DR. LEITMAN: And I would like to introduce Dr. Chitlur to the committee. You are a new member of BPAC, is that correct?

DR. CHITLUR: Yes, I am. Thank you.

DR. DURKALSKI: Thank you. Hi, everyone. This is Valerie Durkalski and I am a biostatistician at the Medical University of South Carolina in Charleston.

DR. RAGNI: Hi, I am an adult hematologist, a professor of medicine at the University of Pittsburgh, and director of the Hemophilia Treatment Center here.

DR. LERNER: Hi, I'm a pediatric hematologist and senior advisor to the director in the Blood Division of NHLBI at the NIH.

DR. LEITMAN: Thank you. Mr. Robert Rees, who is also a new member at BPAC attending his first committee meeting.

DR. REES: Good morning. This is Robert. I am the manager of the regulatory and compliance program for the New Jersey Department of Health.

DR. SCHEXNEIDER: Hello, I am Katherine Schexneider. I am a transfusion consultant at Walter Reed National Military Medical Center, having just moved down to Ft. Belvoir Community Hospital as the director of education training and research, and looking to transition my duties onto a new person in the coming months. Thank you.

DR. LEITMAN: Thank you. Our industry representative is Dr. Toby Simon.

DR. SIMON: Good morning. I'm a senior medical director with CSL Behring.

DR. LEITMAN: Okay, and we are joined by two temporary voting members. The first is Judith Baker.

DR. BAKER: Yes, good morning. Hi, Judith Baker here, public health director for the Center for Inherited Blood Disorders in Orange County which serves as the grantee for the Western States Region 9 Hemophilia Treatment Centers. I'm also adjunct assistant professor at the University of California, Los Angeles, pediatric hematology.

DR. LEITMAN: Thank you very much for joining us, and the site visit chair was Dr. Francisco Bonilla who is a previous BPAC member. He is not present now and will join us at about noon to give us a summary of the site visit, which he chairs.

I am going to pass this over to Bryan Emery who will introduce other attendees to this meeting.

LCDR EMERY: This is Bryan Emery and I am the DFO for the Blood Products Advisory Committee. Good morning. Mrs. Joanne Lipkind is the committee management specialist for BPAC. She is also in the room. Actually, I will start with Dr. Wilson at the table to introduce herself and we'll go -- actually, we will start with Dr. Marks to my left and we'll start there.

DR. MARKS: Hi, this is Peter Marks. I am the center director for the Center of Biologics Evaluation

Research at FDA.

DR. WILSON: Carolyn Wilson, associate director for research at Center of Biologics.

DR. EPSTEIN: Jay Epstein, director of Office of Blood Research and Review, CBER.

DR. ATREYA: CD Atreya, the associate director for Office of Blood Research and Review, CBER.

DR. GOLDING: Basil Golding, division director of Division of Hematology Research and Review.

LCDR EMERY: There are a few people in the audience who I believe are -- Tara Goodin is also here. She is from the Office of Media Affairs and Dr. Scott is on the phone. I'll let Dr. Scott introduce herself.

DR. SCOTT: Yes, Dorothy Scott, Center for Biologics, Office of Blood, Laboratory of Plasma Derivatives.

LCDR EMERY: Dr. Prabha Atreya is also in the audience, and Jennifer Scharpf is in the audience, and there are other members in the audience at this time, of the laboratory as well.

I will now turn the time over to Dr. Marks.

Agenda Item: Recognition of Retiring Members

Peter Marks, M.D., Ph.D., Director CBER, FDA

DR. MARKS: Thanks very much. First of all, thank you everyone today for joining and taking the time to

participate. I just wanted to recognize the four retiring members from the BPAC who will be going, rotating off in September of 2016. I will just say their names and a few of the issues that they worked on.

All of them are rotating off in September 2016 but the first, Mr. Corey Dubin, who is a consumer representative who started in May of 2012 and who was involved in several issues including advice on the blood donor deferral policy for MSM, the discussion of HYQVIA, a subcutaneous immunoglobulin preparation, and also discussed our reentry protocols for donors based on Chagas test results.

The second person is on our call now, which is Dr. Durkalski who started in November of 2012 and who also participated in the discussion of HYQVIA as well as strategies for implementation of serological and nucleic acid testing for babesia and the potential discontinuation of hepatitis B surface antigen testing of blood and blood components intended for transfusion.

The third person, also on this call right now, is Dr. Schexneider who served from November of 2012 and she was involved in discussion of hepatitis E virus and blood transfusion safety, discussed the Octapharma biologics license application for octoplasLG for solvent/detergent plasma -- solvent/detergent-treated plasma -- and also

discussed the reentry of blood donors deferred on the basis of Chagas test results.

Finally, Dr. Toby Simon, who served also from November 2012 and who was involved in a number of discussions including those on strategies for implementation of serological nucleic acid testing for babesia for the appropriate classification of blood establishment computer software, otherwise known as BECS, and also discussed the MSM deferral issue.

So we really thank you so much for your contributions. Without your input, it would be impossible to do what we do, and in coming to some of our conclusions, so we very much appreciate it. Good luck as you rotate off, and we will maybe see some of you in the future again.

Thanks again.

Agenda Item: Conflict of Interest Statement

Bryan Emery, LCDR, Designated Federal Officer, BPAC

LCDR EMERY: All right, I would like to also thank everybody for attending. I'd like to request that everyone check your cell phones to make sure that they are turned off or in silent mode or muted.

Also, I request that you speak clearly and loudly into the phone or microphone so the transcriber will hear you. John Bowers is our transcriber this day.

I will now read the COI statement into the public record. 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, FACA 1972.

With the exception of the industry representative, all participants of the committee are special government employees, SGEs, or regular federal employees from their agencies that are subject to the federal conflict of interest laws and regulations.

The following information on the status of the Advisory Committee's compliance with federal conflict of interest laws, including but not limited to, 18 US 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 the Advisory Committee are in compliance with federal ethics and conflict of interest laws.

Today's agenda includes an overview of the research programs in the Laboratory of Plasma Derivatives, Division of Hematology, Office of Blood Research and Review, Centers for Biologics Evaluation. This overview is a non-particular matter based on the agenda. It has been determined that this overview presents no actual or appearance of a conflict of interest.

In closed session, the committee will review and discuss the report from the FDA site visit team. Toby Simon is serving as the industry representative acting on behalf of all related industry. He is employed by CSL Behring. Industry representatives are not special government employees and do not vote. 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 any products or firms not on the agenda for which an FDA participant has a personal or imputed financial interest, that participant needs to exclude themselves from such involvement. The exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that you may have with the firms that could be affected by the committee discussions.

Thank you. I will now turn the time over to Dr. Wilson to start her first.

Topic 1: Review of the Research Programs in the Laboratory of Plasma Derivatives, Division of Hematology Research and Review, OBRR

Agenda Item: Overview of CBER Research Programs

Carolyn Wilson, Ph.D., CBER FDA

DR. WILSON: Thank you, Bryan, and good morning to

the committee. I want to just start by acknowledging that in addition to Dr. Bonilla, also Dr. Christopher Stowell served as the site visit cochair. So we are grateful to both of them for their leadership during that review.

I will try to give you a fairly high overview of the research program, and my presentation will then be followed by presentations from each of the other levels at the office division and then finally, but really most importantly for today, is you will be hearing from Dr. Scott, the chief of Laboratory of Plasma Derivatives where she will give you an overview of that laboratory's activities, regulatory as well as research.

So on the next slide, I am going to just introduce you to how we view the use of research to advance our ability to advance product development using regulation and science.

So the way we think of it is that a public health need drives the development of a novel product. That product may pose regulatory challenges. Often there is a gap in our full understanding of the science around it to fully be able to evaluate risks and benefits.

As we go forward, then, that's where regulatory science can help address some of those needs through a combination of discovery research as well as targeted development of new tools. So in some cases, that may be,

for example, development of new reference materials that can help evaluate important laboratory tests that are used to evaluate a product. It could be that there is not a good nonclinical model to evaluate the product, and the type of work we do is usually looking across a class of products to help advance a group of products rather than one specific product, which is really what industry does.

So as we generate new science and information from that regulatory science inquiry, that puts us also in a better place to develop regulatory policy and guidance to our sponsors and to inform our decision making based on the best available science.

As we get better data back from the sponsors that's filling some of those gaps, we are in a better position to understand the benefits and the risks of that product. In the end, we hope to license a product that's going to have that positive impact we all hope for that public health need that drove the development.

And it doesn't stop there because we then need to continue with post-market surveillance for adverse events or sometimes there are additional commitments to gain additional efficacy data.

So our staff are composed of what are called researcher-regulators or researcher-reviewers and what these represent are scientific staff members who spend

about 50 percent of their time overseeing a research program, and the rest of their time they are doing the same types of activities as full time reviewers.

What that means is that they are not only reviewing submissions to the agency, but also maybe going out on inspections, writing guidance documents, organizing workshops or advisory committees, and because they are both very active members of the scientific community, going out to their own scientific professional clinical relevant meetings, they therefore are seeing things before they come into the agency and can be sort of proactive in thinking about areas that we need to be preparing for scientifically and understanding better.

But also by having that broader view of the products that are already in-house, they may be able to identify gaps that can best be addressed by our staff to, again, promote a whole class of products going forward. Through this means, this sort of individual who has dual roles, it helps us to make sure that we are integrating the research and the review activities and using our resources in the best available manner.

We don't do this all by ourselves. We do heavily collaborate with the outside and this is from our last year's research reporting database showing that we collaborate really across the country as well as globally.

Especially in the Office of Blood, there is a lot of international engagement through the World Health Organization, for example, as well as other international entities.

This represents a large segment of collaborations with academia as well as other government agencies, nonprofit, state and local government, and some industry collaboration as well that is managed appropriately for conflict of interest.

We have a research reporting database whereby we use this to evaluate our research programs on an annual basis. The PIs develop a report of what's been going on in the past year, their plans for the coming year. This is associated with the budget request. We collect their relevant presentations, publications, other output may be represented by things like employee invention reports or patent applications, licensing, and so on. This is reviewed at multiple levels and it's looked at for relevance, productivity, and quality, and then funding is allocated accordingly.

In addition to that annual sort of management review, we also do a cyclic peer review of every PI every four years and one aspect of that cyclical review is what you will be discussing later today in closed session with is an external site visit, which is peer review by the

experts in the field. That report becomes part of a larger package that goes to an internal peer review committee called the Promotion, Conversion, Evaluation Committee. You may also hear me refer to that as the PCE.

The report that you will be looking at today is a draft report that was developed by the site visit team. It comes to you today for review. You have three options. You can approve it as written, you may wish to amend it, or you may choose to send it back to the site visit team for more dramatic changes.

Once it is approved by the Advisory Committee, then it can be used in a variety of ways. As I mentioned, it becomes part of a larger package for PCE for looking at personnel actions as well as cyclic review. The PIs take the recommendations and the site visit report very seriously in looking at their own research program in future directions. Then management also takes into account the recommendations with regard to resource allocation decisions.

Again, as I mentioned, you have three different choices in terms of how you address the report today.

Quickly want to just review a few new things. We have a peer mentoring program. We moved to White Oak now about two years ago, and a new research management process that we are standing up this year to help enhance most

effective use of our research resources.

The new governance process is around two major new committees, a resource committee that's going to be looking at the annual budget and research planning and this includes not just research resources but resources for the entire center. That's going to be interfacing with the Regulatory Science Council which is going to be looking at center-level goals, office-level objectives, and providing oversight and portfolio review of all of CBER's research activities. Both of these are advisory then to the center director and deputy director.

Already we have had two meetings at the Regulatory Science Council and in our first meeting, we developed four new goals for the center for 2016.

The first is to advance the scientific basis for regulation of our products, to enhance safety effectiveness, quality, and consistency through development and evaluation of new concepts, methods, models, and reagents. The second is to develop and assess nonclinical methods and models with improved predictive value and as feasible, reduce, refine, or replace the use of animals for evaluation of safety and effectiveness of our products.

Third is looking at clinical evaluation related to our products through the use of new biomarkers, large scientific and healthcare datasets, innovative design and

analysis of clinical studies, applying new statistical, epidemiological, and mathematical modeling approaches, as well as considering patient input to inform assessment.

The final one, which is really more sort of an infrastructure and cross-cutting goal, is to prepare for future regulatory and public health challenges through investments in emerging science and technology and develop and sustain varied scientific expertise.

We also developed a new research impact framework which involves both portfolio- and project-level review. So as I mentioned, the Regulatory Science Council is going to be doing portfolio-level review and that's going to be looking for alignment with major center- and office-wide strategic initiatives and priorities. Also asking whether or not the portfolio is helping us to build world class review capability for both current and anticipated pipeline of products we regulate.

Then finally, are we maintaining an agile set of internal capabilities for addressing unexpected, urgent public health needs? If anything, the last two years have demonstrated the critical need for this last point, in addition to the others.

Then we will also be including a peer review component which will complement the external peer review of a site visit but this will be going on on an annual basis

where one fourth of the projects will be looked at individually through an internal peer review committee, and they will be asked to determine whether we are maximally using our unique perspective as regulatory scientists to suggest scientific gaps and questions that are enabling our ability to fulfill our regulatory mission. Obviously, looking at the scientific merit and the PI's historical productivity.

So I will just finish where I started which is a thank you, again, to the cochairs, Dr. Bonilla and Stowell, as well as the rest of the site visit team and to you today as well for your careful evaluation of the site visit report. These external reviews are really important to make sure that the research that we're doing is most directed to the important questions that help us fulfill our regulatory mission.

So thank you very much and I am happy to answer any questions.

DR. MARKS: With no questions, we are going to get Dr. CD Atreya ready in a moment to give his presentation.

PARTICIPANT: I have a suggestion, Dr. Marks. Some of us are not using WebEx but are looking at the slides that were sent to us by Bryan. So could the speaker please say next slide so we know when they are advancing?

DR. MARKS: Will do. Thank you.

Agenda Item: Overview of OBRR Research Programs

CD Atreya, Ph.D., OBRR FDA

DR. ATREYA: Good morning. Thank you all for being here for this important task that is the laboratory site visit review. This is CD Atreya and I will briefly give you the all review of our office that is Office of Blood Research and Review.

Our office mission is to ensure the safety, efficacy, and availability of blood products. This is achieved through the regulation of blood and blood components, plasma derivatives, and analogous products, blood donor screening tests, and other medical devices including software used to test, collect, process, or store donated blood, and retroviral diagnostics.

We have a vision for our -- our functions of the office are to establish policies and standards to assure donor safety and safety purity and potency of blood and blood products. Review of applications for investigational and commercial use of blood products, blood-related drugs, and devices and retroviral diagnostics.

We perform establishment inspections and product investigations with OCBQ and other office FDA counterparts and assist in regulatory compliance actions. We perform health hazard evaluations and risk assessments of blood and blood products. We engage in emergency preparedness --

example, like what happened two years ago, the Ebola, and last year in this now, Zika virus outbreaks.

Then we also do the global outreach as Dr. Carolyn Wilson mentioned and most of the Office of Blood Research and Review is engaged with the WHO programs and I will tell you a little bit more in the latter part of the talk. We also do organize workshops on timely topics and then we provide guidance and document that the research and reviewers take a lead on that. We also conduct research, facilitate the development, manufacture, and evaluation of blood products and retroviral diagnostics.

The vision for research is to support FDA's initiatives and regulatory science including medical countermeasures to facilitate product development through focus on scientific questions critical to effective regulation. We concentrate in areas where our unique role as regulators is most contributory, and we have a provision of an infrastructure for the investigation of product limitations and failures. We also participate in the research programs that advance the innovation in research areas that is going to be enriching the FDA's regulatory science base.

We have resources to do the research and the other tasks I mentioned to you. Our subject expertise ranges from, as you can see from the slide, from virology,

retrovirology, a lot of topics we cover. We have 26 investigators, i.e., that is research-reviewer, initiated programs. Actually these programs are approved by the office and then they are located in two research divisions, also product divisions, under seven laboratories.

And our programs, mainly the research programs, are funded by both internal and external sources. The internal sources include FDA, like Modernizing Science, Medical Countermeasure Initiatives, Critical Path, Panflu, and a lot of other things. Then the external resources include NIH, mostly from the NIAID, NHLBI, NCI, and the Clinical Center of NIH, and also through CRADAs and BARDA.

Our office program has the research goals and there are three goals and then there are 13 objectives that is slated for 2016 through 2020. The goal number one is to assess and promote safety and effectiveness of approved and in-development transfusion products.

Under that goal, we have several objectives. One is the evaluation of ex vivo stored platelets and/or red cells for safety, efficacy, toxicokinetics, development of biomarkers of product quality including Omics-based approaches, and microparticles-associated toxicities, evaluation of the impact of the different manufacturing processes on quality of plasma proteins, and evaluation of the safety and effectiveness of blood substitutes including

hemoglobin-based oxygen carrying solutions, platelet-like products, and related biologics.

Goal number two is to assess and promote safety and effectiveness of approved and in-development injectable products. Under that, we have several objectives. The objectives are development of approaches for predicting immunogenicity of protein based therapeutics based on MHC and mutations in deficient patients and study of immunogenicity of replacement coagulation factor therapies.

The other one is studies of codon optimized recombinant coagulation proteins to assure that increased yield does not affect safety or efficacy. And the evaluation of safety and efficacy of plasma-derived products and their recombinant analogs including measures of potency and risk factors for adverse reactions, and the characterization of virus neutralizing antibodies in immune globulin products.

Goal number three, we have six objectives, and the goal is to assure and promote safety and effectiveness of retroviral and other infectious agent diagnostics, donor screening tests including development of standards, and other devices and technologies used to -- in manufacture and quality control of blood products.

Understanding the mechanism of transmission and pathogenesis of retroviruses, hepatitis viruses, newly

emerging and reemerging blood-borne arboviruses and selected neglected and tropical diseases agents to develop effective strategies to combat these pathogens. And the other one is maintaining blood products and other FDA-regulated products free of the infectious agents of transmissible spongiform encephalopathies and development of strategies for detection and removal of these agents from the blood.

I will just briefly give you, in the next slide, the OBRR research accomplishments. Those are our -- roughly we have 87 publications in the peer-reviewed journals, $2.5 million intramural funding and $1.8 million funding from the NIAID, NHLBI, DOD, and DTRA. We have $1 million funding through CRADAs and three cooperative agreements development agreements CRADAs were established in 2015. We supported 63, roughly, around 65, contract research staff through these funding mechanisms.

As I mentioned to you before, Office of Blood Research and Review also participates globally and for the outreach activities and our office members are either participants or members or observers in WHO initiatives on a list of things as I show you in this slide. The Collaborating Center for Biological Standardization, Expert Committee on Biological Standardization, Blood Regulators Network, Prequalification Program for diagnostics, European

Directorate for the Quality of Medicines and Healthcare, Blood Transfusion sector, International Society of Blood Transfusion Working Groups on Transfusion Transmitted Diseases, Hemovigilance, and Global Blood Safety, and also participate in the FDA, EMA, and Health Canada Blood Cluster.

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

Thank you. Any questions?

LCDR EMERY: Okay, everybody on the phone, we were able to make an adjustment so we can watch the slides on your WebEx. Were there any questions?

All right, if there are no more questions, we are going to go to our third speaker, which is Dr. Basil Golding. He will give an overview of the Division of Hematology Research and Review Research Programs.

Agenda Item: Overview of the Division of Hematology Research and Review Research Programs

Basil Golding, M.D., OBRR FDA

DR. GOLDING: Good morning. My name is Basil Golding. I am the division director of Division of Hematology Research and Review. Before I start, I wanted

to thank, first of all, the site visit team, and second of all, the Advisory Committee for convening today to do a second-level review of our program. Your review and your feedback is very important for us in maintaining the high quality of our research.

So I'm going to slide two. This is just a brief organizational cartoon of our division and you can see that the division is divided into four laboratories. Starting from the left, the Laboratory of Biochemistry and Vascular Biology, Laboratory of Cellular Hematology, Laboratory of Hemostasis, and the Laboratory of Plasma Derivatives, and you see the number of PIs in each laboratory. So my job is to provide you some background of the scope of regulatory products that we review and the scope of research that is related to these regulatory products.

In the next slides, I am not going to be covering the research and review of the Laboratory of Plasma Derivatives. That will be taken care of by Dr. Dorothy Scott in a subsequent talk.

Going to the next slide, I'm not going to go with this slide because it's been covered by previous speakers and relates to the CBER mission.

So the next slide, the scope of regulation and research in our division. As you have heard, research helps solve regulatory problems. The Critical Path was

developed at the FDA several years ago, and the research serves to enhance the expertise of scientific investigators who have review responsibility for these products. Scientific evaluation of biologic products derived from blood include those isolated from blood or plasma and analogous materials manufactured by recombinant DNA technology, including transgenic technology.

In terms of the scope of the regulatory products and starting to talk about the process, the applications that we receive from industry include the whole spectrum of applications that are submitted to the FDA, and include biologics, drugs, and devices. So our reviewers need to be up to date not only with the products but all the regulations and laws related to all these different kinds of products.

Most of the products that we review are diverse complex proteins and in addition, we also review carbohydrate polymers that are used for volume expansion. The decision process is based on scientific data showing safety, efficacy, and purity of the products, and the decision making process involves internal review, presentations to advisory committees, conferences with manufacturers, and workshops.

The review research topics include looking at coagulation products, looking at immunology, and with

protein therapeutics, immunogenicity of the proteins is very critical. Protein structure and function is researched. We also have research related to blood-borne viruses and immune responses to these viruses. Research related to oxygen-carrying compounds, many derived from hemoglobin. And looking at platelet structure and function, and also looking at red blood cell function.

So I'm starting with the Laboratory of Hemostasis on the next slide. I am not going to go through the coagulation cascade. It has two different pathways with multiple protein products. Most of the products that are -- most of the proteins that you see on the slide are regulated by us and many of them have already been licensed either as plasma derived products or as recombinant products.

I am going to go through the different PIs from the laboratory of hemostasis on the next slide. The first PI I'm going to be talking about is Chava Kimchi-Sarfaty.

She works on synonymous and non-synonymous mutations on protein structure and function. For example, FIX. This is also related to codon optimization which is a common strategy used in the manufacture of these products and she has shown that some of the coding optimizations may be beneficial and some may not be beneficial.

She also works on computational and experimental

techniques to investigate the outcome of changes in DNA sequences of therapeutic proteins and is looking at the role of ADAMTS13 in diverse hematologic conditions. As you know, ADAMTS13 is involved in thrombocytopenic purpura

Going onto the next PI, Dr. Zuben Sauna -- he has been working on pharmacogenetic determinants of immunogenicity and has actually been published for algorithms for predicting immunogenicity of recombinant proteins based on HLA and TLR, the receptor, the T-cell receptor 4 proteins that are presented in antigen-presenting cells. He also uses predictors of immunogenicity to reengineer molecules for optimal activity and reduced risk of immunogenicity.

On the next slide, the first PI I am talking about is Mikhail Ovanesov. He has developed and standardized novel global hemostasis assays to assess the pharmacokinetics, pharmacodynamics, and thrombogenicity of plasma protein products to quantitate thrombogenic impurities from FXI-A in FX concentrates and in immune globulin products.

In fact, he has helped resolve a regulatory issue where immune globulin products who were associated with some products -- some products were associated with increased thrombogenicity and he was able to show that it was due to FXI-A and developed assays which were then

transferred to industry. He also studies the mechanisms of action of chemically and genetically modified variants of recombinant FVII-A.

Andrey Sarafanov examines the catabolic pathway of FVIII by mapping epitopes in FVIII light chain for its receptors, which are low-density lipoprotein and low-density lipoprotein related receptors. This research could not only help us understand better how FVIII is catabolized but may lead to improvements in determining -- in making products that have a longer half-life of FVIII. He also has a project characterizing product-related impurities in FVIII products.

In the next slide, I am moving to the Laboratory of Cellular Hematology. This lab reviews red cell components. So it includes red cells, platelets, and plasma, and you can see there is a whole host of types of submissions related to that. I'm not going to go through them one by one, but I am going to go to the next slide to talk about the PIs' research related to these products.

So Dr. Vostal is looking at the evaluation of current and alternative pathogen reduction processes for platelets, looking at the safety and looking for processes which could optimize the pathogen reduction process. One of the projects involves temperature cycled platelet storage methods and this is actually involved in some

clinical studies.

Dr. Simak has been involved in characterization of procoagulant extracellular vesicles and platelet membrane disintegration in DMSO-cryopreserved platelets and liquid stored platelets. So these are types of platelets that are -- could be involved in long term storage and could be very important for the military. He is also looking at the evaluation of effects of engineers and biologic nanoparticles on platelets, endothelial cells and a plasma coagulation system.

Dr. Atreya has his first report of microRNA, a specific microRNA, as a potential regulator of FVIII gene in manifesting the disease phenotype in hemophilia A patients. He is also published on changes on noncoding RNA levels that correlate with storage lesion events in stored red blood cells.

So this is the last laboratory that I am going to cover. It's the Laboratory of Biochemistry and Vascular Biology on the next slide. This cartoon shows you some of the things that they look at. They primarily are looking at hemoglobin oxygen carriers as substitutes for red cells so they are looking at hemoglobin and the toxic effects of it. They're looking at hemoglobin and its interaction with haptaglobin and that complex and how that interacts with macrophages.

On the next slide, the first PI I am talking about is Dr. Abdu Alayash. His projects relate to evaluating the safety and efficacy of hemoglobin-based blood substitutes, exploring human hemoglobin mutants in the search oxidative stability in hemoglobins.

Then we go to the next PI, Felice D'Agnillo, looking at vascular biomarkers of blood-derived product toxicity in cell culture and animal models of endothelial dysfunction, and also looking at the vascular pathogenesis of microbial pathogens.

On the next slide is the PI Paul Buehler. He has been looking at development of preclinical models of vascular endothelial dysfunction to evaluate the safety of aged red blood cells. He looks at the attenuation of pathophysiology in beta-thalassemia, and has a project related to drug-induced hemolysis, hemolytic uremic syndrome, and a TTP-like state caused by intravenous abuse of crushed sustained release opioid preparations. This is obviously in collaboration with people in the Center for Drugs.

So thank you for your attention, and again, thank you for helping us with our research revision review. Does anybody have questions?

LCDR EMERY: If there are no questions, we will go to the phone to listen to Dr. Dorothy Scott give her

presentation. If, Dr. Scott, if you could tell us next slide, we will turn the slides as you talk. Thank you.

Agenda Item: Overview of the Laboratory of Plasma Derivatives

Dorothy Scott, M.D., OBRR FDA

DR. SCOTT: I will indeed and I just want to make sure that everybody on the phone and in the room is able to hear me.

Okay, hold on to your hats because this is a long one. First, I will start with the overview of our Laboratory of Plasma Derivatives Research Program and then we will go onto the specific research and what the principal investigators in our group have been doing.

Next slide, please.

Our mission statement is to meet the public health needs for safe and effective products by performing high quality research that directly impacts the safety, effectiveness, and availability of our products.

By way of background, we are direct descendants of the Laboratory of Hygiene which was started in 1887 and through many iterations, we became the NIH Division of Biologics Control in 1937, then the FDA Bureau of Biologics in 1972 and finally, CBER from 1988 to present. We became a part of CBER.

Our earliest immune globulin licensures occurred

in 1903 when three diphtheria immune globulins were licensed on the same day. The important part of this and reason that I show it is to tell you that we are very historically grounded and we have a very long institutional memory. This has given us a profound understanding of our products as they've evolved and continue to evolve. We also have a great sense of personal responsibility for these products and for the patients who receive them.

Next slide, please.

This is the organizational chart for the Laboratory of Plasma Derivatives. I am the lab chief and Michael Kennedy is the team leader. There are four sections -- the immunology section, host responses section headed by Jennifer Reed, innate immunity section headed by Basil Golding, and the safety and quality section headed by Pei Zhang. The names in yellow are our fellows who are up for convergence to permanent FTEs as a part of the site visit.

Next slide.

We have 39 licensed products. I just want to give you a flavor of their diversity. The immune globulins, these are the general or nonspecific immune globulin as we call them, which are indicated for primary immune deficiency, ITP -- not all products have all the indications -- chronic inflammatory demyelinating

polyneuropathy, multifocal motor neuropathy, Kawasaki disease, and some secondary immune deficiencies.

We also have a host of specific immune globulins. These are enriched for certain specificities for hepatitis B virus, anthrax, cytomegalovirus, hepatitis A virus, tetanus, rabies, vaccinia, varicella, infant botulism, and prevention of newborn hemolytic disease, and that's not all.

Next slide.

We also regulate the antivenoms and antitoxins, and so these are made from animal serum or plasma and they are used to treat coral snake envenomation, rattlesnake envenomation, black widow spider bites, scorpion envenomation, botulism, and digitalis intoxication. We also have the anti-thymocyte globulins which are used to treat certain kinds of transplant rejection, and we have alpha-1 proteinase inhibitor for treatment of emphysema in alpha-1 proteinase inhibitor deficiency.

Next.

This is sort of a list of our regulatory activities between 2011 and 2015 and if you look at it, you can see that we have a fairly, well, we think we have a regulatory burden. That's not a complaint, but we do have a lot of interesting things going on. We've reviewed 414 BLA supplements and 9 original BLAs with 3 more in-house

right now, 33 original investigational new drug applications, and a whole lot of IND amendments.

We participated in at least 115 pre-submission meetings, a number of facility inspections both on-site and by phone as product specialists, and we participate in international studies for reference standards that are used for lot release of our products.

Next.

So I am just outlining a few of our regulatory accomplishments. In particular, we have addressed in the last several years a major adverse advent causing impurities in immune globulin products, including the presence of coagulation FXI-A which can cause thrombosis in patients, from 2010 to the present in collaboration with the lab of Dr. Mikhail Ovanesov in the Lab of Hemostasis. We provided samples and he discovered that this contaminant is highly implicated in some batches which seem -- of immune globulin -- which seemed to cause thrombotic events in patients.

That's since taken care of by the development of standards but also working with the manufacturers. They have been able to understand the root causes and make changes in manufacturing to prevent this contaminant from co-purifying with immune globulin. So nothing has really happened just at one point. There is a long process,

really, to improve the product.

We are also working on effects of hemolytic antibodies that naturally co-purify in immune globulins to find out how those can be minimized also in products, especially for patients who receive high doses of immune globulins.

Just very quickly, again, the licensures that we have overseen in the last several years have included those for counterterrorism products, including the first CBER animal rule product licensure for anthrax immune globulin. We've also licensed botulinum antitoxin. We have a number of orphan products including the antivenoms and varicella zoster immune globulin that were licensed in the past several years. We have licensed a couple of subcutaneous immune globulins, intravenous immune globulins, and another liquid form of the alpha-1 proteinase inhibitor.

Next.

We've developed a number of standards. I won't go over all of these. I think you can read it for yourself. We are involved in with continued standards development, both new standards and qualifying new standard lots for immune globulins and alpha-1 proteinase inhibitors and other treatments.

We planned and chaired workshops related to product safety, including workshops on thrombosis and

hemolysis related to immune globulin products. We've initiated Advisory Committee topics and spoken on those topics in front of the BPAC, and we have participated in national and international scientific and regulatory conferences.

Next.

So the research of course is very strongly related to the regulation and most of the rest of the slides will be devoted to the research portion, but there is always a very close connection.

Next.

This is just a snapshot of the research projects and some of these I will be talking about, others there isn't really time to talk about here, but there is a lot going on in the labs with the principal investigators in our group.

We evaluate neutralizing antibodies in the products including HCV immune globulin and investigational product, Influenza immune globulin, and cytomegalovirus immune globulin, in specific. We developed preclinical models including for smallpox vaccine complications and also for maternal-fetal passive immune therapy.

As you will see from Dr. Golding, he has worked on immunogenicity studies in animal models, the mechanisms of immune responses to Fc-fusion coagulation products.

We've been evaluating the hemolytic potential of different IgE products.

Next.

We have a pretty large project characterizing protein aggregates in products and their impact on potency, safety, and immunogenicity. We've evaluated collection of influenza immune plasma for passive immune therapy with an influenza immune globulin in a pandemic setting. We worked to elucidate the pathogenesis of pulmonary damage from viral double-stranded RNA. This is Dr. Golding's project.

Dr. Reed has been evaluating Zika virus clearance methods along with Dr. Jara Vostal in collaboration with the Lab of Cellular Hematology, clearance methods for blood and plasma donations. And we have been developing assays to measure in vitro functions of anti-Ebola antibodies.

I want to thank you. This is from the garden at White Oak and if you ever have a break when you're here for a committee meeting, I urge you to go out there and enjoy it. This concludes the first part of my presentation. We'll go into detail into some of the research projects in the next presentation. I guess we take questions at the end; is that correct, Bryan?

LCDR EMERY: That is correct. Hold on while I get your second part of this going.

DR. SCOTT: Dr. Marks, are you going to open these

four presentations to questions for the speakers from BPAC members?

DR. MARKS: We certainly will, but I think there was a -- did you want to hold them until after this -- perhaps if there are any general questions on what has been so far -- while we try to get these slides up, if there is one, maybe if someone wants to ask it, we can at least use the time productively.

DR. LEITMAN: So I have a question. This is Susan Leitman. Multiple speakers mentioned in their slides that the research reviewer, research/reviewer, is expected to spend 50 percent of their time on their regulatory and administrative work, leaving 50 percent of time for their research. But in the site visit, the comment was repeatedly made that the time available for research, at least for the PIs, vary from 10 percent to 25 percent. So those are discrepant values.

DR. WILSON: So I used that -- I think that was my presentation; this is Carolyn Wilson -- and I used that as sort of a general average target and it does vary in different parts of the center.

It may vary over time for an individual. So for example, if a BLA comes in and you're chair, you may be doing very little research during that time to meet statutory deadlines. But there may also be other drivers

just overall in terms of the overall workload in a particular segment of an organization that might drove those averages to be different as well. So I leave it to Dot, maybe, to discuss the particulars in LPD.

DR. LEITMAN: Okay, thank you.

DR. SCOTT: I guess I could address that by saying in an ideal world, maybe it would be 50/50 all of the time, but it does depend on the regulatory workload. A lot of folks in our group work more than 40 hours a week and I think they just make up that time so that they can get both accomplished.

DR. MARKS: This is Peter Marks. One of the things that is being undertaken as part of our recent consulting engagement from outside consultants that were -- helped us with the center is we will be trying to capture more completely the balance of work that is done from research and review and essentially try to have fulltime reporting regardless of the number of -- total number of hours spent so we capture all the work that is being done.

LCDR EMERY: I believe we have the slides up.

DR. SCOTT: Okay, what we will do is we're going to look at all four principal investigators' projects, at least the main project that they're working on. I'm going to start with Dr. Golding, but before we do that, I just want to mention that as you've seen, we have a diversity of

products. We also have a diversity of projects.

Our research is really unified by the goal of advancing the scientific understanding of our products and using that knowledge to improve their potency, safety, and efficacy, or to make contributions therefore.

So now I'm going to go on and present research from the three outstanding PIs in my group. I will also present mine. Some of them are here to answer your questions, and their fellows are probably also here in the great room. You may certainly ask questions at the end of this talk.

The first project is Dr. Golding's where he studied immune responses to human FIX and human factor IX mouse Fc-fusion protein in a mouse model, and this is one of the bottom lines. He found that the Fc moiety modulates IgE titers. That is, it influences the formation of allergy-inducing IgE antibodies and rather downregulates that.

Next slide.

DR. MARKS: We are working on it. In the meantime, are there any other general questions? I am just trying to use our time most efficiently.

Oh, there we go.

DR. SCOTT: Perfect timing. The mission relevance of Dr. Golding's -- of this particular project, by way of

background, is that there are new generation coagulation factor replacement therapy products and those include Fc-fusion proteins, including a recombinant FIX protein, Alprolix, and a recombinant FVIII Fc protein.

The person of adding the Fc is to prolong that half-life of these coagulation factors, which makes it much easier for these patients to prevent bleeding but not have to inject themselves as often. The coagulation FVIII and IX have relatively short half-lives which are extended moderately with the Fc-fusion proteins, and Dr. Golding asked whether Fc-fusion, or the presence of the Fc-fusion portion of the protein, altered the immunogenicity of these products. He asked, what kind of immune responses did these elicit and how do they compare in the case of FIX to regular FIX without the Fc-fusion proteins?

Just by way of clinical experience, FIX infusions induce inhibitors in about 3 percent of hemophilia B patients and in rare cases can also induce severe anaphylactic reactions that are IgE-mediated.

Next?

LCDR EMERY: We are working on it. I'm sorry, Dr. Scott.

DR. SCOTT: That's okay. You know, if it turns out to be problematic to switch slides, I am pretty sure that everyone on the phone has a copy of the slides and we

will just proceed in that fashion if we need to. Would you all like for me to go on and they can catch up? Okay, well, as soon as we say it, it happens.

So what Dr. Golding did with this lab group is he set up a model to study the immune responses to these different forms of FIX in a mouse model of hemophilia B. So this is a mouse that's deficient in FIX and these mice receive five weekly IV infusions, either of the human FIX without the Fc portion, or the combination molecule with FIX with Fc portion. Over the time of those five injections, he looked at IgG kinetics formations, as well as inhibitory antibodies or blocking antibodies, IgE, plasma cytokines, and T-cell responses.

He also later looked at long-term memory in terms of anti-FIX IgG and memory B cells. I won't be showing you all of that information. Here you see depicted sort of a general schematic of what FIX looks at and what the FIX attached to the murine Fc looks like. Now of course, for the human product, there's a human Fc, but to make it more relevant to the mouse model, he substituted the murine Fc receptor which in this case is an IgG 2 AFC.

Next.

So here we are looking at neutralizing antibodies to FIX at weeks four and five post-injection or after the fourth and fifth injection of these two different FIXs. In

the black is treatment with the FIX with the Fc. I'm going to call it FIX-Fc. The number of Bethesda units reflect inhibitory antibodies to FIX. What you can see here is that the regular FIX did not give as many, or as commonly, a higher Bethesda unit titer at weeks four or five.

Well, I think we can -- we will just turn to the next slide. So here we are looking at the slide entitled human FIX infusions elicit higher plasma IgE titers and that's indeed what Dr. Golding showed, and that is although they had less neutralizing antibody titers, they had higher total IgE levels compared with the FIX-Fc.

That you see -- actually, you don't see it, so we're going to the next slide. This is the slide entitled FIX-specific immediate hypersensitivity. Can we go to that next slide? Very good.

DR. CHITLUR: Is that the slide -- I'm sorry, this is Meera Chitlur. I am not seeing any of the slides. My presentation is stuck at mission relevance.

DR. SCOTT: Do you have the slides from -- that you were sent by the internet or are you waiting for those?

DR. LEITMAN: This didn't come through the internet. This one was not sent. It would be good to send that. Bryan, this is Susan Leitman. Could you send the copy -- this copy of Dr. Scott's slides to all members of the BPAC?

LCDR EMERY: I will. I'll send it currently.

DR. LEITMAN: Thank you.

DR. SCOTT: So I will continue because I realize now that not everybody --

LCDR EMERY: So, Dr. Scott, this is the second set that we decided not to use. I will send it to the committee right now and we will take a five-minute break and I'll send the second set of slides to everyone. Then they can have it as well. Sorry for the delay.

DR. SCOTT: All right, that should be the slide set with all the initials in it, right?

LCDR EMERY: Correct.

DR. SCOTT: Okay.

(Brief recess.)

DR. SCOTT: Let's go on to the next slide. To really get the amount or to understand whether or not these are specific anti-FIX IgE antibodies, he did a passive cutaneous anaphylaxis test in mice where Evan's blue dye is injected into the tail, and then the potential allergen is injected into the ear.

He injected, of these various mice, either the FIX or FIX-Fc, and in this case he shows a FIX allergy test where FIX was injected into one ear and FIX plus antihistamine into the other. He harvested the tissue and did an Evan's blue dye extraction, but basically what

happens is if there's an allergic reaction, histamine is released. This increases capillary permeability and the dye extravasates from the blood system into the ear, and you measure that dye.

What he showed was that the mice which had received the FIX had more specific anti-IgE antibodies against FIX.

So on to the next slide. His hypothesis is that the distinct anti-FIX immune responses may be due to underlying T cell skewing from between the T-helper type 1 and T-helper type 2 cells. T-helper type 2 cells, abbreviated TH2, release IL4 when they're antigen specifically stimulated, and this causes the production of IgE among other things, whereas T-helper type 1 cells are more characterized by the production of interferon gamma and they may be stimulated by Fc-receptor binding and secretion of antigen presenting cells.

So that is the hypothesis. Next slide?

When he looked T-cell responses in these mice, what Dr. Golding found and in this case it's for mice treated either with the FIX or the FIX-Fc, the FIX-Fc is in the dark bars, that the FIX-Fc treated mice had more specific T-cell responses against FIX characterized by production of interferon gamma, less interleukin 4 and less interleukin 10. So this is a T-helper cell type 1

response, whereas the FIX alone seemed to have induced a T-helper type 2 response based on the fact that IgE was produced.

Next slide?

And I have just already discussed this mechanism, so I won't go over it here. Next slide?

So in terms of future directions, and I realize the title isn't there. Future plans. His group plans to study the effect of Fc-fusion molecules on Fc gamma receptor human primary cells in human cell lines. He can look at activation of antigen presenting cells by the cytokine responses and antigen presentation characteristics of these cells.

He also plans to study the effect of the FIX-Fc on possible downregulation of high IgE responses and this is important to understand whether or not this response actually directly suppresses the IgE-mediated hypersensitivity reaction that's seen with FIX.

Next?

He also plans to study whether molecular engineering of the Fc can be done that may reduce immunogenicity and enhance inhibition of immune responses. Then at the same time improve binding to the Fc neonatal receptor, which would further increase half-life. He is also planning to study the effect of Fc-fusion molecules on

humanized mice.

And now we will switch completely to the next project, by Pei Zhang. Is anybody else having very odd lettering coming up on some of their slides? I am missing some words and letters on my slides. I just wanted to make sure that everybody else's on the line is okay with their slides. I'm through the WebEx.

DR. MARKS: What I see is good.

DR. SCOTT: Okay, I have a hard copy. So I'm fine too.

Now I'm going to introduce you to the laboratory of Pei Zhang, who is a principal investigator and the fellow who has done a fair amount of this work, Lu Deng. There are others in the lab also who have contributed to the project, and this is a study to improve antibody-mediated neutralization by HCV-specific immune globulins.

Next slide? You'll have to pardon me, while I reorganize my slides, because they are not coming through at all well.

Okay, so in terms of mission relevance, HCV infection is a major public health issue worldwide, and it also presents a safety concern for blood and blood products, at least historically, but we have to continue to be vigilant.

Dr. Zhang's research program is intended to

facilitate the development of effective HCV-specific immune globulin products, for example, the development of potency assays, to help ensure the safety, effectiveness, and availability of HCV immune globulin products and to contribute towards the efforts that are being made to develop an HCV vaccine.

Next slide.

And I'm going to summarize his major accomplishments. The first among these is the identification and characterization of HCV envelope glycoprotein E2 epitope, and you see depicted here HCV, the HCV E2 protein. The epitopes that are involved in antibody-mediated neutralization and non-neutralization of the virus. So there are some antibodies that bind but don't neutralize, and even interfere with neutralization by other antibodies, and that is depicted in the section as well.

They also demonstrated structural flexibility and dynamics in HCV E2 epitopes that form the basis of neutralization and non-neutralization of the virus. So based on studies of the antibodies in HCV patient blood samples and HCV-specific immunoglobulins, they identified and characterized three important epitopes on the envelope protein E2, epitope I, epitope II, and epitope III, and the studies on epitope II specifically suggested that antibody

can use bifurcated mode of action to interact with the epitope with a specific tertiary structure, and these different tertiary structures of epitope II are presented on the viral surface, and those might determine the antibody specificity and consequently the outcome of neutralization versus non-neutralization, and this becomes important, because you don't want a lot of non-neutralized in your interfering antibodies in an HCV immune globulin.

Their study suggested a mechanism for antibody interference, and we will go on from that to the next slide.

They also identified two conformational states of the HCV epitope II called an open and closed state, which you can see here. HCV E2 does exist in these two conformational states based on biochemical and x-ray crystallographic structural studies done at Dr. Zhang's lab.

So for virus, for the virus, for the advantage of the virus, E2 can present itself in different forms during the infection, which can be transient and allow it to escape host immune surveillance which provides a virus with a growth advantage, but for the host, the transient forms may not be able to stimulate robust immune responses to control the virus. So these are very important things to understand about hepatitis C virus and how it evades the

immune response and also how difficult it might be to make an HCV immune globulin that only neutralizes the virus.

Next slide, please.

Dr. Zhang's group has also established a working model for the interface formed between the HCV E2 epitope and the host receptor CD81. They combine crystallographic and molecular docking techniques to establish this model, and it indicates that the flexibility of epitopes on the E2 protein might have a great impact on the virus receptor interaction, thus serving as a vulnerable site for development of antibodies and vaccines.

So again, this is work in progress, but they are currently understanding which exact conformational epitopes might contribute to this binding and how they are expressed and when they are expressed.

So next slide.

In conclusion, the epitopes on HCV E2 have different local conformations and different specificities for neutralizing and non-neutralizing antibodies. E2 exists in at least two conformational states, the open and closed conformations. The existence of natural variance in the epitopes, such as the A524V in epitope III, can modulate antibody binding without affecting the virus entry process, is consistent with the escape mechanism of HCV from antibody-mediated neutralization, which is common.

And this structural information may be useful for development of tests to monitor the potency of HCV-specific immune globulins.

Next slide.

In future studies, structural flexibility and dynamics of the E2 protein are noted to not only affect the optimal presentation of antigenic sites of interest but also provide a potential mechanism of immune evasion. So specifically, he plans to combine crystallographic methods with H/D exchange mass spec to capture and analyze conformational changes in E2 and, using HCV cell culture, determine whether conformational changes in E2 are actually correlated with host receptor interactions and whether antibodies targeting specific conformations can effectively neutralize the virus.

So we are going to go on to Dr. Reed's project, one of the very new projects, and one she has been working for some time. I'll talk about the older project first, which is related to increasing U.S. preparedness for potential expansion of smallpox vaccination. Just by way of background, smallpox vaccination can cause some side effects, particularly in people with immune deficiencies or people with atopic dermatitis, and in both cases, those consequences can be life-threatening.

The only licensed treatment for either

progressive vaccinia or eczema vaccinatum is vaccinia immune globulin. Clinical studies are generally lacking, because these are very rare diseases currently, but there are questions when people have gotten eczema vaccinatum how much vaccinia immune globulin to give them, what else one might give, and how to really interdict that process.

So the first project within this category called project one is to -- the relevance is to improve preparedness for the emergence of eczema vaccinatum and to use the data generated to support rational development of vaccinia immune globulin treatment with and without co-therapeutics. The second project is to create a platform for testing novel therapies that target either host or viral pathways with special relevance in the skin.

Next slide.

I have already mentioned that human eczema vaccinatum can be life-threatening, and the main point here is that widely available animal models for eczema vaccinatum are needed and are currently not available. These could be used to measure responses to vaccinia immune globulin treatment and to identify co-therapies.

So that is the need, and for the second project, to provide a detailed analysis of innate antiviral responses of keratinocytes, which are the first to see vaccinia virus or smallpox virus for that matter, and to

identify keratinocyte host pathways that are targeted by vaccinia and the viral factors responsible for disease. In other words, how is the keratinocyte affected and can this information be used to develop new therapies to prevent the spread of this virus in susceptible people?

Next slide, please.

Major accomplishments. Dr. Reed did develop an atopic dermatitis eczema vaccinatum model by initiating development of mice that are deficient in STAT3 and filaggrin, and both of these are deficiencies that are seen in some forms of atopic dermatitis in patients who get skin infections commonly.

What you see here with the picture of the mice is a mouse that did not receive smallpox vaccination. That is on the left, and on the right one that did, and if you look closely, you can see especially on the right ear that there is a skin lesion but also on the face and other parts of the body. So this mouse actually did develop a vaccinia infection of the skin. This is the first time really that such a model has been developed that is accessible that can be used by others.

She also discovered when she looked at these lesions that the TGF beta family ligand Activin A was higher in infected skin compared with what we saw in previous vaccinia models, and she used topical TGF beta

receptor inhibitors and found that those synergized with vaccinia immune globulin to lower the viral titers in the skin of vaccinia. So that is currently being pursued.

Next slide.

She and her group also demonstrated that STAT3 and filaggrin themselves facilitate programmed necrosis of vaccinia-infected cells in vitro, and this is a host-protective strategy that actually the first cells to get infected die quickly and release danger signals and they don't really perpetuate virus much themselves by dying early and sending off these signals.

She identified pathways that are triggered by vaccinia in these infected keratinocytes that are involved in the process of early cell death called necroptosis, and this is just a picture of uninfected keratinocytes in the top row and vaccinia infected keratinocytes to show one among several of these mediators, DAI, that are involved in necroptosis and are stimulated in the presence of vaccinia infection.

Next slide.

So her plans are to evaluate combined therapies in the mouse model, including VIGIV, antiviral treatments, and TGF beta receptor inhibitors. Those are given topically in the mouse model. And to test whether excessive production of wound healing factors in skin

remodeling actually promotes a viral niche in skin. In the second project she plans to use high throughput screening with siRNA to identify additional host factors that can control or limit viral growth in keratinocytes.

Next slide.

Now we are going on to a relatively new project obviously that Dr. Reed has initiated along with Jara Vostal in the Lab of Cellular Hematology who I already mentioned. This is an ongoing project. They are very early results, but I think it is good because it demonstrates that we are capable of rapidly addressing new public health concerns using our expertise in products and that this has special value. So this project is Zika virus inactivation in whole blood via UV irradiation and photosensitizers.

Next slide, please.

The data she obtains may help identify means to increase the safety of blood transfusions in the near term for high risk patients, such as pregnant patients in Zika-endemic areas, should they need transfusion, and the data may also demonstrate ways to optimize existing pathogen reduction methods for whole blood applications.

Next slide.

So what she set out to do was to test licensed pathogen reduction methods for Zika inactivation potential

in red cells and whole blood preparations. So she tested two commercial methods using licensed conditions, UV-A and psoralen derivatives, and UV-B and vitamin B, and the idea was to identify whether optimization might increase virus inactivation.

I am not going to show you this, but part of this project is to determine the impact of the inactivating methods on red blood cell integrity and oxygen carrying capacity and to later perform a proof of concept transfusion transmission rodent model to find out how effective these inactivation methods are in an in vivo experiment.

Next slide?

So these are early results, showing that UV-B with or without vitamin B inactivates Zika virus in whole blood with acceptably low hemolysis levels, but it is a far reduced efficacy compared with Zika virus inactivation in plasma. But the early data suggests that optimization of pathogen reduction might be feasible in the system and might increase Zika virus inactivation.

So what you are seeing is the treatments on the left-hand column, the amount of logs of virus reduction in the middle column, and basically UV and with or without vitamin B can cause about five logs of reduction in whole blood, but you can see that this is even better for plasma.

Plasma is clear and it's easier for the UV-B to have an effect.

Next slide.

Her future directions or current directions anyway are to further optimize the licensed pathogen reduction methods by evaluating different blood storage materials that have a better UV transmission profile and increase surface area. They also plan to increase the dose, that is, the amount of time, of UV irradiation exposure with chill-down breaks, and of course test the impact of this on red cell integrity as well as on Zika virus reduction.

She also plans to evaluate Zika virus transmission from transfused pathogen reduction treated versus untreated blood in interferon gamma susceptible mice that can acquire Zika virus infection.

Next slide.

So I think we are all very pleased with how quickly this Zika virus project and others in the Office of Blood and the Office of Vaccines have gotten off the ground, and you may look forward to hearing a lot more about this in the future.

Finally, and thank you very much for your patience, the last center project, which is in my lab. I am going to be talking about two projects. The first one

is related to hemolysis, which is a long-recognized adverse event associated with immune globulin infusions, particularly at high doses. Despite the fact that there is a lot release limit for isoagglutinins in the product. In the past few years, it was noted that certain products have higher reporting rates for hemolytic complications than others, although they all meet the lot release specifications using the direct hemagglutination assay, and this, which we abbreviate DHAT method, is a binding assay but not a functional assay.

So we wondered whether a functional assay would give us somewhat different results or differentiate between products that had a higher reporting rate of hemolysis versus those that had a lower reporting rate. So what we did and what I'm going to show you is that we developed a complement-mediated functional assay, which we call the CDHA, for hemolysis and immune globulin. We are also investigating the mechanisms of action for intra- and extravascular hemolysis related to immune globulins, and we have developed new reference standards for the DHAT and for CDHA methods in collaboration with NIBSC.

This work addresses the goal of ensuring the safety of biological products and developing and evaluating reference materials and standards and assays for product assessment.

Next slide.

The major aims were to develop a complement-dependent hemolysis assay and to identify IGIV characteristics that are associated with a propensity to mediate intravascular hemolysis, particularly characterization of the isoagglutinins in IGIV with respect to antibody subclass, and to collaborate with national and international regulatory authorities, both in a regulatory and a research fashion and to develop these reference standards.

Next slide.

It's a wordy slide, but I think it can go pretty quickly, because we were able to establish a practical and reproducible complement dependent hemolysis assay protocol for our products, which expands our ability to evaluate IGIV lots in suspect hemolysis cases and also to characterize the products, and what we did was rather old-fashioned, but we made some changes to increase assay sensitivity.

We studied the effect of papain treatment, removal of irrelevant IgG molecules, and use of neat serum. We defined and optimized pH conditions for the assay. We evaluated interference by excipients, and we -- I think this is one of the things that will help others take up these assays is we improved assay-to-assay and intra-

laboratory consistency by optimizing collection and freezing methods for red cells, and these are little red cells you see in the tube, droplets of red cells, and developing a unit scale collection method to obtain large batches of human serum with intact complement, which has always been a sticking point for these kinds of assays and the reproducibility.

We did demonstrate a correlation between the CDHA and DHAT methods, but the reproducibility is better for the CDHA than for the DHAT and the sensitivity seems somewhat better as well. We characterized hemolysin-mediated IgG subclass specificity in recombinant monoclonal anti-A antibodies, where we found that IgG 3 was the most active, and in products where we actually found that IgG 2 seemed to have the most activity, followed by IgG 1, which is interesting and we are pursuing it.

Next slide, please.

So some of the accomplishments are our participation in establishment of a WHO International Standard for anti-A and anti-B in serum, generation, in collaboration with NIBSC, of a stock preparation of reference reagents as a positive control for anti-A and anti-B that can be used for CDHA and DHAT characterization products.

Specifically, it's very hard to find immune

globulin products with very high anti-A and anti-B titers, or lots, I should say, a lot, and we were able to find one and this has quite high titers and it's going to be very useful for developing and understanding assays in providing a high titer standard.

We also, as a part of all of this, co-organized a public workshop with NHLBI and the Plasma Protein Therapeutics Association to discuss strategies to address hemolytic complications of immune globulin infusions, and these include not just testing strategies but also manufacturing strategies and a better understanding of how these isoagglutinins seem to co-purify with other immune globulins more in some products than in others.

Next slide.

So our future aims are to test implicated product lots identified through adverse event reporting and characterize the potential hemolysis risk also of investigational IGIV products and those under evaluation for licensure. So in other words, we can do this research testing in our own laboratories and share those results with manufacturers as we and they consider the manufacturing method.

We will go on to confirm and investigate the role of IgG subclasses in IGIV-mediated hemolysis. We plan to develop an anti-A, B assay to measure these dual-specific

antibodies that occur especially in blood type O donors in implicated and non-implicated lots. They are hypothesized to have more potent hemolytic abilities than a typical anti-A or anti-B antibody.

We are planning to develop a cell-based hemolysis to model extravascular hemolysis using activated and quiescent macrophages in antibody-sensitized RBCs as targets in the presence of complement to address the hypothesis that inflammation is an underlying predisposition to development of hemolysis in people who receive high doses of immune globulin.

We hope soon to publish and share the established CDHA protocol with manufacturers and international regulatory agencies in NIBSC, and we want to explore the possibility of extending the CDHA methodology to other CBER-regulated blood products.

Next slide.

Finally, I'm going to talk very quickly about the efficiency of plasma collection for manufacturing of influenza immune globulin during a pandemic, and this is a completely different type of project obviously, which is focused not on safety, but rather on potential efficacy of influenza immune globulin and how this might be manufactured in the study on the pandemic.

Next slide.

So as you all know, influenza is considered a pretty big public health problem even in normal years, and it causes a number of deaths every year in the United States. Neuraminidase inhibitors, which are the mainstay drug treatment, may fail due to drug resistance or may be in short supply during a pandemic. Likewise, vaccine supplies have been in short supply earlier on in pandemics due to the manufacturing timeline required and manufacturing capacity.

Now, on the other hand, passive immunotherapy with immune globulin products is effective for prevention and treatment of many viruses. We don't know about influenza, but from animal studies we have an idea and from limited human studies that IGIV enriched for influenza antibodies might prevent or ameliorate influenza.

But the question that was asked is how can collection of influenza immune plasma be optimized, because you need this immune plasma to make an immune globulin during a pandemic, and we were fortunate to be able to analyze samples from a collection program that was intended to collect hyper-immune influenza plasma for manufacture of an influenza immune globulin, and we were also able to evaluate a new test method that has potential for plasma screening.

Next slide, please.

So in 2009, Baxter Corporation and Baxter BioLife initiated a study to ask if they could manufacture a FLUIGIV during a pandemic, and in this case, they put up posters and sent out postcards to their regular donors asking them if they would like to volunteer, whether or not they had been infected with influenza, pandemic influenza, or been vaccinated for it, prior to their next donation. These histories were not verified and the donations were not tested, to save cost and to save time.

The plasma collected from these donors who volunteered such histories was segregated and manufactured into two IGIV lots, which were shown to have high pandemic H1N1 antibody levels compared with contemporaneously manufactured lots that didn't have this special plasma, and the FLUIGIV was shown to be effective with a pre-exposure prophylaxis in SCID mice. It took, however, 5 to 8 months from collection of the plasma to release of the final product, which was not used, by the way, in clinical studies. The idea was really to see what they could collect and to study it in animals.

So our future aims were to just use the hemagglutination inhibition test to determine how well this collection strategy identified donors with high titer antibodies in the absence of testing or detailed questioning and also to develop a rapid virus free method

to test plasma donations for influenza neutralizing antibody using Surface Plasmon resonance. I won't have time to show you that second part today.

So next slide. Actually we are on slide 40. I have shown the major aims. So we will go on to major findings. What we were able to show is that in the pandemic setting, the plasma selection really could have been improved if only we had known what the titers were, because high titer donations were prevalent in the self-reported vaccination group to a greater extent than the convalescent or random donor group. So there is actually a large number of donors with lower titers.

But what we would want to make a hyper-immune globulin that is as potent as it can get is probably the really high titer donors. On the other hand, low titer donations were most prevalent in the random donor group, followed by the convalescent and vaccinated donors.

So of course with that collection program as it was, it naturally was often donors with a self-identified history of influenza or influenza vaccine exposure that actually probably didn't have influenza and may not have even been vaccinated or the vaccination wasn't very effective in those donors.

In the low titer groups, of course, there are plenty of those in the convalescent and vaccinated donor

subsets. So this just shows you that it could be improved, and that's not surprising, because the plasma couldn't be tested at that time, and what we have done is developed a Surface Plasmon resonance assay that shows -- uses the concept of showing binding inhibition with serum antibodies of the H1 hemagglutinin to cognate glycan receptor by this immune sera, and that does correlate with hemagglutination inhibition assays.

So the results suggest strategic improvements that could increase collection of the influenza immune plasma during a pandemic, not only testing but perhaps by having more detailed questioning and establishment of in-house assays for testing potency of FLUIGIV plasma in products.

And finally, in future directions, next slide. We plan murine studies to determine the efficacy of pre- and post-exposure prophylaxis by FLUIGIV. We will use variations in dose and timing, and we are also planning to look at the in vivo effect of anti-H9, anti-H5, and anti-H2 antibodies that are found in many IGIV products. So look at whether or not they are effective against virus challenge with reassortment viruses, and publication of the H1 glycan binding inhibition studies on human sera.

Next slide.

I really apologize to the committee and thank

you for your patience and interest and time. I know we have gone over time. I also want to thank the office, the center, and the FDA for their financial support and broad support of these kinds of studies and all of the work that you have seen and more, and I believe that what they have been able to do is help us contribute to the science that is really the bedrock of our regulatory activities.

I thank you all very much, and I guess we are ready for questions.

Agenda Item: Questions for the speakers

DR. SIMON: I have a question. This is Toby Simon. Is it okay to go ahead? You sort of really got my interest there, as you might guess, on the last on the influenza immune globulin, but I wondered -- I think the research is certainly good and appropriate -- had you any though how you would deal with that 5- to 8-month delay between collection and immune globulin in the event of a real pandemic?

DR. SCOTT: Well, yes, there are certain places where there may be some flexibility. So even though this was intended to be pretty fast, obviously, by moving around the logistics of manufacturing you could make it faster; the question is also how much time would be used just waiting for the lot release test to be completed and where there may be flexibility there. I would say the collection

program went very rapidly, because many, many people wanted to make these donations and that could actually probably be even quicker if more centers were involved in such a project.

So those are the two places I see, because actually from -- you know better than I from collecting the plasma, the actual manufacture is only going to take a few days. It's everything that needs to go before and the testing that needs to come after that takes such a long time.

My own opinion is this could probably be done in 3 months, and it ideally would be done between the first and second wave of a pandemic. Sometimes there is a third wave.

DR. RAGNI: This is Margaret Ragni. I wonder if I might ask a question. First of all, I thought that your presentation was outstanding. I thought it was just excellent. I was interested in the Fc FIX and your immunogenicity studies and wondered if in hemophilia it is a group with hemophilia A that are more likely to have inhibitors whether you were going to do studies in a similar fashion with FVIII Fc. Not IgE of course. I am just talking specifically IgE. It's the IgE is not heard of the inhibitor formation in hemophilia A.

DR. GOLDING: So this is Dr. Golding. So yes,

that's a very important question, and we are starting to look at that. So yes, definitely. We want to look at the Fc FVIII as well in terms of immunogenicity. So we will follow the same kind of protocol that you saw for the Fc FIX, first looking in mice to see what we can identify in terms of types of antibodies, and then look to see at the underlying mechanism first in mice and then once we have that information we can switch to humans and look in vitro at human cells and the effect of Fc FVIII on human cells.

DR. RAGNI: That is very important. Whenever Fc is bound to any protein, my understanding is that it induces the Tregs which make the Fc -- makes the protein, makes the immune system tolerant to the protein to which it is attached, and there are some mice data through Biogen and their preliminary studies and we have been doing some studies in humans and it's very exciting and I think it is something that has great potential in terms of the patients with hemophilia using these products.

DR. GOLDING: Yes, I agree, and I'm familiar with that work and we are actually collaborating with Dr. Strouse at Johns Hopkins looking at Fc, binding to Fc gamma receptors, and looking to see if we can optimize the Fc binding in a way that would induce T regulatory cells that would actually induce tolerance. Yes, we are thinking along very similar lines.

LCDR EMERY: I was going to say Dr. Epstein at the Office of Blood Research Review has a statement to make.

DR. EPSTEIN: This is back to the prior question about rapid response. We actually have a collaboration ongoing with World Health Organization. This is in the wake of the Ebola outbreak on an initiative that they call platform technologies, and one of the technologies that has been under discussion is a system for small-scale production of up to 20 units of plasma to make an immune globulin concentrate. So if you were to combine the ability to rapidly screen for the antibody of interest with the ability to make small-scale concentrates, you might be able to react extremely quickly to this kind of epidemic.

I agree with largescale fractionation. Probably you are limited between wave one and wave two.

DR. LEITMAN: This is Susan Leitman. I have a follow-up question to what Dr. Ragni asked about immunogenicity of the Fc VII and IX fusion proteins. I imagine that FDA requested clinical immunogenicity data from the manufacturers when they first submitted their license application. So they had -- there were paired studies of subjects receiving conventional recombinant factor and Fc fusion. I can't recall from the publications what the immunogenicity data showed, but there was the

clinical data on inhibitor formation. Is that correct?

DR. GOLDING: Yes, definitely, for both products we had the standard clinical trial and as you probably know, what we look at are patients, previously treated patients, PTPs rather than PUPs, and we, based on the incidence or the rate of inhibitor development in previous studies, we determine statistically whether the product is approved or not. But these are relatively small studies, because these are relatively rare diseases. So you are talking about 80 patients in the FVIII study, and I don't remember for sure, but I think it was somewhere around 50 patients in the Fc FIX study.

No inhibitors were observed in either of those studies, but I would point out that you probably have to do much larger studies to find a low rate of inhibitors that may be different between the Fc and the regular FIX, and we will look for -- we are looking at the moment in animals and in vitro, but hopefully larger clinical studies will be done, especially in PUPs, and we are understand that the PUP population, previously untreated population, is much more sensitive to the development of inhibitors, but those are always done as -- they started during the licensing process, but they all followed up after licensing. So we are looking eagerly to see what kind of follow-up studies show in terms of immunogenicity.

DR. EPSTEIN: Susan, it is Jay Epstein. But one fine point. These are not paired controls. They are in essence single arm studies looking for inhibitor rate, and we have a statistical criterion for acceptance or rejection.

DR. RAGNI: But no inhibitors were expected in any of those PTPs. So it doesn't answer the question. We really need PUPs to do the study. There are several ongoing prospective studies to do that.

DR. GOLDING: That is correct, and we are eagerly looking for the date.

DR. RAGNI: That is part of post-licensing surveillance is to request that data in much larger numbers of patients.

DR. SCOTT: It's to request it in PUPs, previously untreated patients.

DR. LEITMAN: Susan Leitman again. Data were shown on Zika virus inactivation in red cells using pathogen reduction techniques of either UV-A plus psoralen or UV-B plus vitamin B, but there's no licensed pathogen reduction for red cells. The only licensed techniques are for plasma and platelets, correct?

DR. REED: This is Jennifer Reed replying to your comment. Hi. Good morning. Yes, that's right. We don't have a licensed technique for inactivation in red cell

preparation. So we would be using techniques which have been shown to work in plasma and adapting them as best we can to red cells just to see if we can find a way to maybe utilize them in a rapid response kind of methodology.

So far, as you can see, the UV does seem to be working, and the addition of vitamin B increases the Zika reduction, but we need to utilize blood bag that material which increases UV transmission, and also we are working out the optimal temperature and the size of the bag in order to make sure that the UV is appropriately reaching the target. Does that answer your question?

DR. LEITMAN: Yes, it does.

DR. BASAVARAJU: This is Sridhar from CDC. Another question about the Zika presentation regarding the strain that you used. Did you use other strains, or was it just the Cambodia strain?

DR. REED: The first strain that we had access to was the Cambodia strain which was rapidly sent to us by UTMB. We had since come up with additional strains. We have a Panama strain that we are growing and we have one strain from UCFA(?) that we are also growing.

The limiting factor there is just getting a high enough titer stock with. So we are almost there with both of those. We are not anticipating a huge difference between the inactivation profile of Cambodia versus those

more recent strains, but we should have that data set shortly.

LCDR EMERY: Are there any questions? All right.

Agenda Item: Open Public Hearing

LCDR EMERY: At this time I will take a moment to look around the room to see if there are any members of the public that would like to speak in open public hearing.

I see nobody in the room at this time. So we are going to close the open public session at this time, and we will take a break before going into closed session. In the meantime, Dr. Toby Simon from industry will be leaving, and Dr. Dorothy Scott will also be getting off the phone and off the computer so that we will go into closed session, and we will be waiting now for Dr. Bonilla to come on line so we can go into closed session.

Thank you.

(Whereupon, the open session adjourned.)