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Center for Biologics Evaluation and Research (CBER)
Vaccines and Related Biological Products Advisory Committee
154th Meeting

OPEN MEETING

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Great Room Salon C
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CALL TO ORDER/INTRODUCTIONS

MS. HUNTER-THOMAS: Okay. Dr. Monto, I think we are ready to start.

DR. MONTO: Well, I would like to welcome the members, consultants to this meeting of the VRBPAC. I think our opening event should be introduction of the committee members. I would like Serina to call each individual by name and they can tell us where they're from and what they do, in the usual manner of these open meetings. Serina?

MS. HUNTER-THOMAS: Sure. I'd be happy to, Dr. Monto. We'll start with Dr. Holly Janes?

DR. JANES: Good morning. I'm a biostatistician. I work at the Fred Hutch Cancer Research Center. I do clinical trial design and conduct, mostly in the area of HIV, but also in other infectious diseases. Thank you.

MS. HUNTER-THOMAS: Thank you. Dr. Myron Levine? Mike, are you there? Okay, we'll circle back to him. We'll go on down to Dr. Cody Meissner?

DR. MEISSNER: Yes, I'm here. I'm a pediatric infectious disease specialist, and I have interest primarily in respiratory viruses and vaccines in general.

MS. HUNTER-THOMAS: Thank you. Dr. Paul Offit?

DR. OFFIT: Yes, I'm here. I'm a professor of pediatrics at the Children's Hospital of Philadelphia and University of Pennsylvania's School of Medicine. I'm a pediatric infectious disease specialist also with an interest in vaccines.

MS. HUNTER-THOMAS: Thank you, Dr. Offit. Dr. Shane? Andrea Shane?

DR. SHANE: Yes, hi. Good morning. I'm Andi Shane. I'm an associate professor of pediatrics at Emory University in Atlanta with an interest in infections and vaccines associated with enteric infections.

MS. HUNTER-THOMAS: Thank you, Dr. Shane. Dr. Geeta Swamy? Dr. Swamy? Circling back to Dr. Mike Levine? Okay, checking in with Mr. Sheldon Toubman?

MR. TOUBMAN: Yes, good morning. I'm here. I am an attorney at New Haven Legal Assistance Association with a specialty or expertise in representing folks on Medicaid. I really have no technical knowledge, but I'm the consumer representative for the committee.

MS. HUNTER-THOMAS: Thank you. Dr. Melinda Wharton?

DR. WHARTON: Good morning. I'm an adult infectious disease specialist, and I'm Director of the Immunization Services Division at the Centers for Disease Control and Prevention in Atlanta.

MS. HUNTER-THOMAS: Thank you. Dr. Leonard Friedland?

DR. FRIEDLAND: Hi. Good morning. My name is Dr. Leonard Friedland. I'm a pediatrician and a vaccine researcher at GlaxoSmithKline Vaccines, and the alternate industry representative on this committee.

MS. HUNTER-THOMAS: Thanks, Len. Is Dr. Hana El Sahly on the line?

DR. EL SAHLY: Hi. This is Hana El Sahly, Baylor College of Medicine.

MS. HUNTER-THOMAS: Hana, we lost you. Dr. El Sahly? Okay, we'll circle back to you. We lost connectivity with Dr. El Sahly. Is Dr. Mike Levine on the line?

DR. LEVINE: Yes, he is. Good morning.

MS. HUNTER-THOMAS: Can you give us an intro, Dr. Levine?

DR. LEVINE: Yes, I'm the associate dean for Global Health Vaccinology and Infectious Diseases at the University of Maryland, School of Medicine.

MS. HUNTER-THOMAS: Thank you. Dr. El Sahly?

DR. EL SAHLY: Hello. Can you hear me?

MS. HUNTER-THOMAS: Yes, we can hear you.

DR. EL SAHLY: Hi. Hana El Sahly, Baylor College of Medicine about infectious diseases and with research in clinical vaccine development.

MS. HUNTER-THOMAS: Thank you. And, Dr. Monto, as the acting chair today, it's your turn.

DR. MONTO: Arnold Monto. I'm professor of

epidemiology and work in the epidemiology and prevention of mainly respiratory infections here at the University of Michigan.

MS. HUNTER-THOMAS: Thank you. Dr. Spearman, are you on the line? And Dr. Geeta Swamy, are you on the line?

DR. SWAMY: Yes, I'm here. Thank you.

MS. HUNTER-THOMAS: Can you give us a quick introduction, please?

DR. SWAMY: Sure. Thanks, Serina. Hi, this is Geeta Swamy. I am associate professor in obstetrics and gynecology at Duke University, and my area of expertise is in maternal immunization, perinatal infection.

MS. HUNTER-THOMAS: Okay. Thank you. We like to do a quick introduction of the FDA staff that's in the room, starting with you, Jerry?

DR. WEIR: Jerry Weir. I'm the director of the Division of Viral Products.

DR. CHUMAKOV: I'm Konstantin Chumakov. associate director for Research at the Office of

Vaccines.

DR. GRUBER: Hi, this is Marion Gruber. I'm the director of the Office of Vaccines.

DR. LEVIS: Hi. Robin Levis, deputy director for the Division of Viral Products in the Office of Vaccines.

DR. WILSON: Carolyn Wilson, associate director for Research Center for Biologics.

DR. PEDEN: I'm Keith Peden, chief of the Lab of DNA Viruses, the reason why we're all gathered here today.

MS. HUNTER-THOMAS: Thank you very much. If you don't mind, Dr. Monto, I'll proceed with reading the conflict of interest statements that we can get started with the presentation.

ADMIN ANNOUNCEMENTS, COI STATEMENT

DR. MONTO: Please do. And just to remind everybody, as Dr. Peden said, the reason we're here today is to review the Laboratory of DNA Viruses. That's our major agenda item. Please go ahead, Serina, and read the conflict of interest.

MS. HUNTER-THOMAS: Good morning, everyone. The Food and Drug Administration is convening today, November 8, 2018, for the 154th meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

The following information on the status of this advisory committee's compliance with Federal Conflict of Interest laws, including but not limited to 18 U.S. Code Section 208 of the Federal Food, Drug and Cosmetic Act, is being provided to participants at this meeting and to the public for the record. The Conflict of Interest statement will be available for public viewing at the registration table outside.

During the open session, the committee will hear an overview of the research program of the Laboratory of DNA Viruses, Division of Viral Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research. This meeting is determined to be a nonparticular matter and there are no affected firms identified for this topic.

Therefore, no prescreening of the members and consultants was conducted. Based on this agenda topic, it has been determined that the overview presentations of the research program do not pose an appearance of or actual conflict of interest.

Following this open session, in accordance with 21 CFR section 14.27b, implementing 5 U.S. Code 552BC6, the Center for Biologics Evaluation and Research is authorized to hold a closed session. The purpose of this closed session is to review matters of which the disclosure would constitute an unwarranted invasion of personal privacy of permanent CBER staff with regards to their personnel actions and/or staffing decisions.

Dr. Leonard Friedland is serving as the industry representative. He is employed by GlaxoSmithKline. It is to be noted that industry representatives are not special government employees and are not voting members of the committee. Hence, they do not participate in the closed sessions and do not have voting privileges.

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

This concludes my reading of the Conflict of Interest statement for the record for the open portion of this meeting, and I'll hand it back over to Dr. Monto. Thank you.

DR. MONTO: Thank you, Serina. I think the next speaker is Dr. Carolyn Wilson, who is the associate director for research at the Center for Biologics, and she'll tell us about the overview of the research and the site visit process at CBER. Carolyn.

OVERVIEW OF RESEARCH/SITE VISIT PROCESS, CBER

DR. WILSON: Yes. Hi. Thank you, Dr. Monto, and welcome everyone. I first want to start by thanking Dr. Monto and Dr. El Sahly, who served as co-chairs for this particular site visit, and to just

remind the members of the advisory committee that we really rely on your willingness to service the community by participating as chairs or co-chairs of these site visits as they pertain to your expertise. I hope the sound is better on the phone than it is in the room. There's a funny echo, which I don't know if we can do anything about.

Anyway, so I will continue, and I apologize for those of you who've heard some parts of this talk before, but just to orient you that CBER regulates a variety of complex biologic products and certain devices. Obviously, you're familiar with the area of vaccines and things like therapeutic probiotics; but we also regulate allergenic products, xenotransplantation products, certain human tissues, cell and gene therapies, blood, blood components, and blood derivatives.

We consider science as critical to the ability to regulate and advance product development. This graphic is one that -- again, I apologize to those of you who've heard my talk a million times. You've seen

this before. But I continue to use it because I think it's instructive, that really everything comes back to a public health issue that drives the development of a novel product to address the public health need.

However, when those novel products come to us as an agency for review, they may pose challenges in the regulatory decision-making environment. For example, perhaps we don't have an animal model to evaluate the proof of concept or the mechanism of action. Maybe reference materials are needed, or other tools or assays are required to be able to evaluate these products. That's where regulatory science, through a combination of discovery and targeted development of new tools, really helps to inform regulatory policy making and decisions.

As we get better data and better guidance to sponsors, then in turn they submit back to us improved data that allows us to address those gaps that we had at the beginning so that we can make benefit/risk decisions, informing the licensure of a product that we hope is going to be both safe and effective and

have a positive impact on that public health issue. It doesn't stop there. We also have a very robust post-market surveyance, in particular, looking for safety signals, but also often includes additional efficacy evaluation as well.

We view the research program as benefitting the Center and its regulatory mission, by making sure that our researcher reviewers, who are actively engaged in the review process as well as the research, make sure that we have the appropriate relevance, expertise; and that the research program is timely and useful in the kinds of problems that they're addressing as they're seeing them in the regulatory environment. We also feel that the output of the research fosters rational policy and decisions, so that we make all of those decisions based on sound science, law, and public health impact.

It's also important to allow us to prepare for future innovative products and public health challenges. As I mentioned previously, it is also very targeted in developing tools and data that are

available to all stakeholders, and support development of product classes. Finally, we recruit and maintain highly trained scientists with the necessary expertise that is important to enable review of regulatory submissions.

The expertise in the center is varied, but obviously focused in areas of importance to the products we regulate. We have a number of applied technologies and analytical biochemistry, including NMR mass spec, flow cytometry, high-throughput sequencing, and appropriate bioinformatics and IT tools to support that. As you would imagine, we have a lot of microbiology expertise, immunology, biochemistry, molecular, cell and developmental biology, and more recently we've been expanding into tissue engineering and microphysiologic systems. Obviously, epidemiology, biostatistics, and bioinformatics are also critical components of our expertise.

We moved to White Oak lab facility here at the FDA consolidated campus in 2014. This allowed us to

develop expanded space for core facilities in certain areas like flow cytometry and microscopy, as well as high-throughput sequencing and the bioinformatics support for that. And then we continued a number of biotechnology-related core support. We also have a state-of-the-art vivarium, which is important for providing imaging in a variety of modalities, animal BSL-2 and BSL-3 facilities, and procedure rooms, and transgenic derivation.

We also have a peer mentoring group that is available to all PIs. It's a monthly meeting, and we always identify one senior PI to informally lead the discussion, and any of a variety of issues can be addressed there.

We obviously can't do everything we need with given the broad regulatory responsibilities that we have. We can't do that alone, so we actively collaborate, obviously, across the United States, internationally -- oops, sorry, this trigger's a little sensitive. Internationally, as well as in a variety of different sectors. As you can see, the

largest piece of that pie is with academia, but we do have collaborations in a variety of different sectors.

We manage our research through a variety of different processes at the center level. About two years ago, we stood up a regulatory science council to oversee the development of research goals at the center level and approve office goals and objectives. You'll hear more about that in the next talks. It also has been useful in helping to develop a research evaluation framework. We do evaluation of our research programs annually through management review, and then a combination of internal and external peer review.

To just drill into each of those a little bit more, our research goals are currently four major areas: advancing the scientific basis for regulation of biologics, human tissues and blood, by first developing and evaluating technology, reagents, and standards to inform CMC; developing and assessing nonclinical models and methods predictive of clinical performance with respect to toxicity and

effectiveness; and improving clinical evaluation pre- and post-licensure through use of big data, innovative designs and statistical, analytical and modeling approaches. And then finally, but also very importantly, is preparing for future regulatory and public health challenges.

The evaluation framework I mentioned, we consider that to be along four major categories: mission relevance; dissemination, which is obviously presentations and publications; scientific impact, which is really the uptake of that scientific information by the community and regulated stakeholders. And then also, how are we applying the research in terms of regulatory practice and enhancing our regulatory mission.

Again, just to summarize the research evaluation, the management review is in three different areas. We do annual review down at the project level. We have centerwide horizon scanning, which occurs once every several years, done by the regulatory science council. And we do officewide

portfolio review at the program level. The peer review is an internal review that we do at the project level.

We do one-fourth of all projects every year, so that each project is reviewed once every four years, through an internal peer reviews process. This external site visit is our review at the programmatic level. Then we also have an internal peer review for personnel actions called CPERR, the Center Promotion and Evaluation for Researcher Reviewers, and that's at the PI level.

The site visit is really critical for reviewing senior staff fellows and staff fellows, who are in the service fellowship program, as well as permanent staff who are referred to as principal investigators and staff scientists. And the senior staff fellows and principal investigators are independent scientists, whereas the support scientists are either referred to as staff fellows, visiting associates, or staff scientists. This is a really critically important element of the overall evaluation

of our research programs.

The site visit report that you'll be reviewing in the closed session -- and just a reminder not to discuss any of the specifics of that report or the personnel actions in the open session. That is a draft report that the site visit team developed for your review. You have three options in your review of that report. You can accept it as written, you can amend the report, or in rare cases -- actually, at least in the ten years I've been doing this, I've never seen it, but it is an option at your disposal -- or you can reject the report and send it back to the site visit team.

Once approved by the full advisory committee, the final report is used -- oh, sorry. This is an old slide. This is by CPERR, the new acronym for personnel actions. The PIs, obviously, take all of your scientific input very seriously to help improve their research programs; and management, obviously, takes it into account when making resource allocation decisions.

I'll finish with where I started with a large thank you to both the site visit team and to you today for your input into our research programs. It really is critical to the work we do. And I'll stop there and happy to take any questions.

MS. HUNTER-THOMAS: If there are no further -- does anyone have any questions on the line? Okay. Hearing none, we'll move on to Dr. Jerry Weir's presentation. Thank you.

OVERVIEW OF DVP

DR. WEIR: Thank you and good morning. I'm going to give a brief overview of the Division of Viral Products within the Office of Vaccines Research and Review.

If you look at the second slide, this gives an organizational chart of the Office of Vaccines. Marion Gruber is director, Philip Krause is the deputy director and there are three divisions within the office. Two of these, on the left and the center, are called product divisions, and they have research functions -- missions. One is Division of Viral

Products, which is the subject of today's VRBPAC, and then there's also a Division of Bacterial, Parasitic, and Allergenic Products.

If you go to slide three, the OVRR Regulatory Mission and Portfolio is designed to protect and enhance public health by assuring the availability of safe and effective vaccines, allergenic extracts, and other related products.

If you go to slide four, our regulatory challenges, as you might expect, are significant. Being an Office of Vaccines, of course we have an emphasis on safety because many of the products -- most of the products we use are for mass use, often universal. The recipients are healthy individuals, often children. And sometimes we have extremely short regulatory cycles for review and acting on submissions.

Examples of this include seasonal influenza vaccines, but also our response to emerging pathogens, most recently things like Ebola, but also Zika, pandemic vaccines. Also, a lot of our vaccine

products are old, and there's a push underway to use new innovative technologies to improve a lot of these products. And of course, we think that research plays a critical role in the regulation of vaccines.

If you go slide five, this summarizes the OVRR research goals. All of our goals are designed to ensure safety, efficacy, and availability of the products that we regulate. And all our research is designed to fit within these basic research goals.

If you go to slide six, this is an organizational chart of the Division of Viral Products. We have seven laboratories that are roughly, but not perfectly, arranged around the products, the vaccines that we regulate. The subject of today's site visit and previous site visit is the Laboratory of DNA Viruses with Keith Peden as lab chief.

If you go to slide seven, this summarizes the Division of Viral Products' mission and functions. We regulate viral vaccines and related biological products, ensuring their safety and efficacy for human

use. But we also try to facilitate the development, evaluation and licensure of new viral vaccines that positively impact the public health.

If you go to slide eight, this lists our major responsibilities. We have a lot of responsibilities in fulfilling our mission. Part of it is to review and take action on investigational new drugs and biologic license applications or BLAs and other pre-marketing activities. We also are responsible for BLA supplement review, lot release review, and other post-marketing activities. Our staff participates in manufacturers' inspections, both pre- and post-licensure. And we have an extensive role in consultation with other public health agencies, for example, the WHO. And last but not least, the staff conducts research related to the development, manufacturing, evaluation and testing of viral vaccines.

If you go to slide nine, this describes the role of research in the Division of Viral Products. As you've already heard in the CBER overview, our

research and laboratory activities are also designed to complement the regulatory mission. We address issues related to regulated viral vaccines, but we also try to anticipate, and address, issues related to the development and evaluation of new viral vaccine products. Sometimes these research projects approach and address general issues applicable to many products or product classes. Sometimes they focus on specific product issues, for example, correlates of protection necessary for understanding efficacy evaluation, things like animal models necessary for animal rule implementation.

Slide ten is a quick snapshot of the staff and budget overview for the recently concluded FY18. The division has 75 full-time equivalents, but this staff supplemented by approximately 40 contractors in our ORISE program. These are postdoctoral and postbac fellows. The division budget for the last year was fairly substantial, and it's actually been steady for several years. We got a basic operating budget of about $4.8 million. We received additional targeted

FDA support of about $1.4 million. Then we had a fairly substantial external support, through grants and contracts, that the principal investigators received. This was another $1.8 million.

If you look at slide 11, this shows a quick snapshot of the laboratories and the staff in them. The IOD or my direct office, there's six FTEs and the rest of the FTEs are distributed among the different labs. There's not the same number in everyone because there are a different number of principal investigators in the different laboratories.

And, finally, I think this is the last slide, to conclude with the site visit evaluation. This is important to us because it helps -- it is a review of the programs and an assessment of progress on the different projects being pursued since the previous site visit. As I already mentioned, it's important for individual review for people considered for conversion and promotion, and of course we always value your input for future directions that the different investigators have proposed. Thank you.

MS. HUNTER-THOMAS: Thank you, Dr. Weir. Now moving on to the last presentation, Dr. Keith Peden, who is the laboratory chief, or principal investigator, of the Laboratory of DNA Viruses. Dr. Peden.

OVERVIEW OF LDV

DR. PEDEN: Good morning. As I've been introduced, I'm Keith Peden, chief of the Lab of DNA Viruses. And I'd like to thank everybody on the line for participating in this meeting. And I'd also like to thank, of course, Dr. Monto and El Sahly for being the chair and co-chair for our site visit.

I'm in a rather privileged position in this lab because I have very excellent PIs who work in this lab. I'd just like to acknowledge that Jerry Weir, Phil Krause, Andrew Lewis, and Haru Murata are very excellent people and it's a pleasure to be the administrative chief of those people. I'd just like to acknowledge them.

All right, I'd just like to indicate some changes since the last site visit in 2013. Dr.

Haruhiko Murata was appointed as Acting Principal Investigator in the lab. Jerry Weir continues to be a principal investigator in LDNAV with his other duty, as you heard, as Director of DVP. He did relinquish his position as Acting Chief of the Laboratory of Pediatric and Respiratory Viral Diseases, as Dr. Ye took over that position. And Phil Krause continues to be a principal investigator in the lab. His position as Acting Deputy director of the Office of Vaccines Research and Review was made permanent, so congratulations to him.

This is the organization of the lab where we had our site visit in May of this year. As you can see, there's a Unit of Viral Latency, Phil Krause, PI, Unit of Adventitious Agents and Cell Substrates, Andrew Lewis, PI, Unit of Viral Gene Expression, Jerry Weir, PI, and Unit of Cell Biology and Molecular Genetics, and I am PI. And the new unit, is Unit of Molecular Virology, Haruhiko Murata is PI. And the people under their respective PIs are listed. One change is Wei Tu is moved from my group, into Haruhiko

Murata's group, so it looks a bit more even.

What is our regulatory responsibility? As you heard from Jerry, the Office of Vaccines Research and Review has the responsibility for regulation of prophylactic vaccines against bacterial and viral diseases. The Division of Viral Products has responsibility for prophylactic vaccines against viral diseases. The Lab of DNA Viruses' major responsibility is for vaccines against diseases caused by DNA viruses, DNA viruses as vaccine vectors for other diseases; and with other labs we collaborate in that effort, in DVP, and in fact act as co-consultants to other offices. And also, infectious diseases caused by other viruses and members of the lab involving influenza, Ebola virus, and Zika virus regulation.

The regulation of all stages of development of viral vaccines, with a special focus on DNA viruses. And this goes, as Jerry said, all the way from Pre-INDs, INDs, master files, biologics license applications and supplements, post-marketing

commitments, and lot-release testing and evaluation, so it covers the whole gambit.

And the type of vaccines that we are involved with, you might expect, is viral vaccine, both live-attenuated and inactivated, subunit vaccines produced in e-coli or baculovirus in insect cells, recombinant proteins, virus-like particles, DNA vaccines; and recently we've received several submissions for messenger RNA vaccines, a new and exciting introduction.

Over the years, we've been involved in licensing vaccines, all the way from herpes zoster in 2006. And now in the last one, in 2017, was a shingles vaccine, which is a recombinant gE protein with the adjuvant AS01B, and that's manufactured in CHO-K1 cells, a tumorigenic cell line that perhaps would not have been possible many years ago. But, with that tumorigenic cell substrate and the MDCK cell substrate, I think the work done in DVP has allowed us to license those vaccines.

How does our research program help the public

mission? Well, research programs of each PI give them, and their staff, the expertise to provide expert and informed guidance to industry on all aspects of vaccine development and manufacturing. Importantly, when a crisis arises in vaccines, as it has over the years, we can help resolve those issues. The most recent was the finding in 2010 by an academic lab. A porcine circovirus contaminated a rotavirus vaccine. But because we had talented scientists, mainly in Dr. Krause's group, we were able to provide data to your committee, and that convinced them that there were no safety concerns raised by the finding.

In addition, our research is useful in the developing reagents and assays to assist sponsors in pandemic preparedness for potential pandemic influenza, such as those caused by H5N1, H1N1, or H7N9, and in fact other additional ones that are coming down. And Jerry Weir's lab is instrumental in targeting that.

Other issues that our lab addresses -- and this is associated with vaccines and vaccine/cell-

substrate safety. And Andrew Lewis' group is involved and has been doing that for many years now. His group assesses whether the quantitative tumorigenicity assays can assist in cell-substrate characterization. And recently, has been looking at whether microRNA profiling of cell substrates can be used as a surrogate for tumorigenicity assays.

In my group, we're also working on cell-substrate safety. Our group has been addressing, over the years, whether there are any safety concerns with the residual cell-substrate DNA that inevitably contaminates the vaccines. And also, determining whether understanding the mechanism of tumorigenesis assists in estimating risks associated with using such cells for vaccine manufacture.

Dr. Murata, as the new PI, he is also investigating vaccine efficacy and vaccine safety, and he has established a program in human cytomegalovirus, and is measuring antibody activities against the viral glycoproteins in serum and plasma and therapeutic immune globulins. He's also developing ways to

facilitate assessment of tumorigenicity. I'll say a bit more about each of these when I talk about the individual investigators.

So, the first, I just mentioned briefly about Jerry Weir. If I'm wrong, Jerry will correct me. The goal of his research effort is to facilitate the development and licensure of vaccines for high priority viral diseases, by addressing issues important for product evaluation and characterization. For example, facilitate the development and evaluation of seasonal and pandemic influenza vaccines.

This is just parenthetically that we're in the Lab of DNA Virus; but it is important to recognize that as new viruses and new issues arise, PIs and our scientists adapt to the crisis at hand. Jerry not only continues to work on other viruses, but he established a major program in influenza for the reasons -- they're obvious -- with the pandemic influenza problems. So, he identifies and evaluates viral antigens and vaccination strategies that are important for the development of a protective

immunity.

Part of the group's work is the development of alternative potency assays for seasonal and pandemic influenza vaccines. And this is for seasonal and pandemic potency. And the development of high-yield candidate vaccine viruses to improve vaccine manufacturing. And support for influenza vaccine manufacturing by improving reagent development and characterizing manufacturers' working seeds, such as alternative methods for preparing potency antiserum and antigenic testing of working seeds. So that's among the research that Jerry's lab does.

Phil Krause, his unit is called the Unit of Viral Latency. Phil is an expert in herpes viruses and applies that to his work currently. He has two sections. His work is divided really into two sections. He likes to discuss his work on herpes viruses in two different ways. He does developing molecular methods for the detection of the genomes of latent or persistent viral infections, but this has moved into the identification of methods for the

detection of adventitious agents. And so, Phil has been instrumental in developing methods to detect adventitious agents that perhaps would not have been detected by other methods.

But, in addition, he has his work on herpes viruses and determine the strategies viruses use to become latent and subsequently reactivate to understand how this affects disease caused by viruses. And he considers this important for understanding what vaccines must accomplish. You must accomplish a vaccine against herpes virus that deals with this virus becoming latent. It's important for better understanding of live-attenuated vaccines that could establish latency, and important for understanding latency in the context of cell substrates, since a new cell substrate might have a latent virus within it.

So, when Phil started detecting these viruses, he developed methods to extract nucleic acid. This is either in a capsid, if it's a viral particle, and so you can enrich for nucleic acids for viruses. Then he also developed a non-specific PCR method to detect

these unexpected viruses, such as developing the degenerate oligonucleotide-PCR methods.

But more importantly, and recently, with the advent of next-generation sequencing, massively parallel sequencing, how can these technologies be used to detect adventitious agents? That's still an issue that we're wrestling with in DVP and elsewhere in FDA. Phil's lab has been developing algorithms to analyze data, so he is a critical component of the activity to assess whether next-generation sequencing can be used in a regulatory method.

For HSV latency and recurrence, HSV preferentially establishes latency in certain neuronal subtypes. Latency occurs when lytic genes are inhibited. Virus replication and spread and reactivation occur when lytic genes are expressed. The outcome infection in any given neuron represents a contest between the forces that promote replication and those that promote latency.

And recently, his work of one of his talented staff scientists, Shuang Tang, has been studying HSV

protein ICP27. They've shown that ICP27 regulates alternative splicing and polyadenylation of HSV and cellular genes. This novel finding might provide insight into the pathogenesis of HSV. Phil's lab was the first lab in the world to identify this product; and so that just shows how talented his lab is.

The Unit of Adventitious Agent and Cell Substrate that Andrew Lewis is principal investigator. Andrew has been studying vaccine cell substrates for many years. When it was clear, in 1998, that additional cell substrates were required for the manufacture of the next generation of vaccines, these cell substrates were either tumorigenic often or derived from human tumors. The question was, for us, how does OVRR address the presumed safety issues with using such cells while retaining the public confidence in vaccines?

This was a big issue and our scientists and DVP have been trying to wrestle with these questions; because there was a perception -- and still to some extent is -- that using tumorigenic cells represents a

risk. So, we had to deal with this if we needed to use cell substrates for the new generation of vaccines. So, the potential safety issues with cell substrates; it was, could be the presence of unknown oncogenic viruses in the cells or the residual DNA, which could be an oncogenicity or infectivity. So, studies were initiated in DVP to address these issues; and Andrew and I have been working together for quite a long time on this issue.

Andrew's been working on VERO cells and MCDK cells; because VERO cells are used to produce several licensed vaccines and many vaccines in the pipeline. MDCK cells are used to isolate candidate influenza virus vaccine strains. And as we hear, that MDCK cells are also used to produce the cell produced influenza vaccine.

So, both cell lines were derived by spontaneous immortalization. VERO cells are not tumorigenic but can become tumorigenic by passage in culture. MDCK cells are tumorigenic, at least the ones used for vaccine manufacture.

And again, I'd like to just go back to 2000, when we discussed the VERO cells to this committee; and it was recommended to us that we should set up a program on VERO cells, to understand how these cells became tumorigenic. We, at the time, thought this is rather an ambitious recommendation, but in fact we did work on this study. I think now we have a fairly good idea how VERO cells become tumorigenic.

But because early passages of neither cell line are not available, the Lewis lab isolated new cell lines from the African green monkey kidney and dog kidney -- the precursors of these same type of cells in the VERO and MDCK respectively -- to understand the processes that bring about, affect the spontaneous immortalization, to identify any risk factors that might be there.

It turned out that the lines from AGMK and the canine kidney cells did become tumorigenic on passage in culture. Spontaneous immortalization is accompanied by changes in microRNA expression profiles. Whether microRNA profiles can be used as

biomarkers for the acquisition of a tumorigenic phenotype is being investigated by the Lewis lab.

On the next PI, Haruhiko Murata, Unit of Molecular Virology, Haru decided that since there were nobody working on cytomegalovirus in DVP, he thought he'd move into this field. As we know, human cytomegalovirus is a major public health concern. In immunocompromised individuals, reactivation/reinfection can lead to severe disease. It's a leading cause of congenital infection, leading to hearing loss and neurological and cognitive deficits. There is no licensed vaccine against CMV, although several candidates are being assessed. So, we thought that having an expert in cytomegalovirus would assist in the regulation of these new vaccines.

Haru has been developing high-throughput virus-neutralization assays for CMV, using a qPCR-based endpoint assessment. That type of endpoint assessment is used by several of us in DVP. But first of all, he needed to generate a CMV that was epithelial/endothelial-tropic virus, because most

viruses you get are lab-adaptive viruses, and they grow on the fibroblast, but this is not the cell that's used for CMV to infect humans.

So, what they did was take a lab-adapted fibroblast-tropic virus and passed it in cells to restore the open reading frame that was necessary for the virus to enter epithelial/endothelial-tropic cells. Then they used that to quantify neutralizing antibodies, both after commercial antibodies, but also the anti-CMV/HCMV products that you can buy and what are used clinically.

Recently, he’s been developing in-vitro assays to study virus entry and cell tropism. So, he wants to know which proteins are involved with entry in various cell types. CMV, being a huge virus, is not such an easy virus to manipulate with molecular genetics; so Haru is using a reductionist approach to see whether you can use other viruses to address these entry issues.

Now, because Haru's been working with Andrew Lewis and me for quite some time, we have continued

some collaborative studies on tumorigenicity and DNA oncogenicity. Haru recently has been evaluating whether extracellular matrices, such as Matrigel, influence the detection of tumorigenic cells, and whether such reagents can assist in the regulation of cell substrates. He's doing that with Andrew and me. He's also continuing to evaluate immune-defective mice for the detection of DNA oncogenicity.

Finally, I'll give you a little bit of an overview of what we do. Our goals/objectives are to identify potential risk factors associated with the use of novel cell substrates, particularly tumorigenic cells or cells derived from human tumors. We want to develop quantitative assays to measure risk factors, determine whether these risk factors can be mitigated, for example, by testing for their presence or removal during vaccine manufacture, et cetera. And I'll say, this has been a sustained collaboration since about 2000 with Andrew Lewis.

Our current projects are continuing to develop animal models to assess the DNA oncogenicity, so to

assess whether cell-substrate DNA can be oncogenic. Determination of whether identifying the mechanism of neoplastic transformation can assist in estimating the risk of using such cells for vaccine manufacture. If the dangers are genetic, if they are due to epititious agents or if they are epigenetic, the risk factors can be assessed from that. For example, if the cell changes are epigenetic that causes a cell to become tumorigenic, then that represents a very minimal risk, if at all, for using those cells for vaccine manufacturers, since it's not possible to transfer those events to a recipient.

We've also been involved in establishing of high-throughput microneutralization assays, to quantify neutralizing antibodies against human pathogenic viruses, again, using these quantitative PCR readouts. We've been looking at Ebola virus and Zika virus and plan to look at dengue and perhaps MERS and SARS down the road. With Ebola, of course, we don't use the virus, we use a VSV Ebola virus hybrid. Zika, because it's a VSL2 agent, you can use that

virus. But for MERS and SARS, VSL3 agents, we're attempting to use VSV as a backbone for that as well.

I'd just to finish with the outcomes of the research on DNA. In vivo assays have been developed that can detect the oncogenic activity of cellular oncogenes. Several rodents have been identified that can detect the oncogenic activity of our ras/myc plasmid at below one nanogram level. Most people think that was impossible when we started this work, but it is true; you can detect one nanogram of the activated rats and make dual plasmid.

We use newborns of CD3 epsilon mouse, SCID mouse, p53 mice, and newborn rats. And they can all detect about one nanogram of DNA or below.

These results have been used by DVP to estimate risks from residual DNA, and to develop recommendations to sponsors for the amounts and size of DNA. But DNA oncogenic studies have reservations. For one thing, they're unlikely to detect the oncogenic activity of an activated-dominant oncogene in cellular DNA, due to the dilution. For example,

the genome size of a mammalian genome is three times ten to the ninth base pairs; an oncogene might be ten to the fourth base pairs. So, there's a huge dilution up to about a million-fold difference. So, one microgram of a plasmid would be several kilogram or so of DNA. This makes the probability of detecting very, very low. And that's in fact what we found.

But, even if this is possible detected activated oncogene and cellular DNA, only a subset of oncogenes score positive in these assays. We've assayed several oncogenes. For example, c-Myc does not score positive in an assay by itself, but it does with rats. Importantly perhaps, human papillomavirus, E6 plus E7, do not score positive in any assay, in any animal model, that we've detected. It needs rats as a complementing oncogene. Therefore, it seems possible that not all oncogenes are going to score positive. Therefore, we've decided that perhaps the best approach is to limit the size and the amount of the residual DNA in vaccines, and that's the approach we've been taking.

I'll finish there and thank you for your attention. Again, if you want to ask questions, you may. So, I'm finished.

DR. MONTO: Thank you so much, Keith. Do we have questions from the group? Hearing none, the next question, Serina, is what we do next? We're scheduled to have a break, and when do we reconvene?

MS. HUNTER-THOMAS: We ended a little early with Dr. Peden's presentation. Is a 10-minute break more reasonable to the majority of the members on the phone as opposed to a 15?

MEMBERS ON THE PHONE: Sure, yes.

DR. MONTO: Literally, do we know of anybody who is going to be requesting participation in the public section?

MS. HUNTER-THOMAS: At this time, there are no public speakers, no requests for public participation.

DR. MONTO: Which is another reason we'll be moving more quickly in the afternoon.

MS. HUNTER-THOMAS: Correct. We can reconvene at I'd say 12:05. Is that fair?

DR. MONTO: 12:05 Eastern. That's okay with me.

MS. HUNTER-THOMAS: Okay. We'll reconvene at 12:05, everyone. Thank you.

DR. MONTO: Ten minutes. Thank you.

OPEN PUBLIC HEARING

MS. HUNTER-THOMAS: Dr. Monto?

DR. MONTO: I'm here.

MS. HUNTER-THOMAS: Alrighty. It's 12:05 so I think we can get started.

DR. MONTO: Let's get started. Do we have any public speakers at this point?

MS. HUNTER-THOMAS: We have none, so we can proceed with you and Dr. El Sahly's review of the report.

OPEN MEETING ADJOURNED