Food and Drug Administration
Center for Biologics Evaluation and Research

133rd Meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

May 8, 2013

Rockwall II, Conference Room 1033
5515 Security Lane
Rockville, MD

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service. Accordingly, the Food and Drug Administration makes no representation as to its accuracy.

Proceedings by:

CASET Associates, Ltd.
Fairfax, Virginia 22030

CONTENTS

Call to Order and Opening Remarks Robert Daum, MD, Chair	1
Conflict of Interest Statement Donald Jehn, MS, FDA	2
Topic I: Presentation of Laboratory of DNA Viruses, Division of Viral Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research	8
Overview of Research/Site Visit Process Carolyn Wilson, PhD, FDA, Center Biologics Evaluation and Research (CBER)	8
Overview Division of Viral Products, OVRR Robin Levis, PhD, FDA	22
Overview Laboratory of DNA Viruses Keith Peden, PhD, FDA	28

P R O C E E D I N G S

Agenda Item: Call to Order and Opening Remarks

DR. DAUM: I will call the meeting to order and turn the floor over to Don Jehn in a moment. I must say. This is one of my FDA VRBPAC committee chair activities and that is that we get to hear during regular VRBPAC meetings from while doing the science that they are talking about, but to actually get a chance to view the science and go behind the scenes and here that roughly hear at regular VRBPAC meetings is really very well informed by laboratory experience is a treat. I am delighted at this opportunity to do it. Let's get going and turn the floor over to Don for some opening remarks.

MR. JEHN: Thank you, Dr. Daum. This is Don Jehn, the designated federal officer for today's meeting of the Vaccines and Related Biological Products Advisory Committee. I would like to welcome you to the 133rd meeting of the advisory committee.

Today, we have a session that is opened to the public followed by a closed session. The meeting is described in the Federal Register Notice of April 5 of 2013.

Before proceeding further, I would like to take the final roll call of the committee members on the phone

today just so that we have that for the transcriber officially. Dr. Daum.

DR. DAUM: I am here.

MR. JEHN: Dr. Durbin.

DR. DURBIN: Here.

MR. JEHN: Dr. Schoolnik.

DR. SCHOOLNIK: Here.

MR. JEHN: Dr. Tacket. I know she joined us. Maybe she has her phone on mute. Dr. Air.

DR. AIR: Yes, I am here.

MR. JEHN: Dr. Marcuse.

DR. MARCUSE: Here.

MR. JEHN: Dr. Tacket, did you just join us?

DR. TACKET: Yes, I did.

MR. JEHN: Thank you. Dr. Kester.

DR. KESTER: Here.

MR. JEHN: Dr. Piedra.

DR. PIEDRA: Here.

MR. JEHN: Dr. Tsai.

DR. TSAI: Here.

Agenda Item: Conflict of Interest Statement

MR. JEHN: Great. Before proceeding further, I need to read the conflict of interest statement for this meeting. The Food and Drug Administration, FDA, is convening today's meeting of Vaccines and Related

Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all participants of the committee are special government employees, SGEs, or regular federal employees from other agencies that are subject to the federal conflict of interest laws and regulations. The following information on the status of this advisory committee's compliance with federal conflict of interest laws including, but not limited to 18 US code section 208 of the Federal Food, Drug, and Cosmetic Act are being provided to participants at this meeting and to the public. FDA has determined that members of this advisory committee are in compliance with federal ethics and conflict of interest laws.

Today's agenda includes an overview of the research programs in the laboratory of DNA viruses, Division of Viral Products Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, FDA. 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. Dr. Theodore Tsai is serving as the industry representative acting on behalf of all related industry. He is employed by Novartis Vaccines. Industry representatives are not special government employees and do

not vote. This conflict of interest statement will be available for review at our table here.

We would like to remind members, consultants, and participants that if discussion involve any products or firms not on the agenda for which an FDA participant has a particular or personal or imputed financial interest, the participant needs to exclude themselves from such involvement and the inclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that you may have with firms that could be affected by the committee discussions.

Thank you for your patience. Dr. Daum, I turn it over to you.

DR. DAUM: Mr. Jehn, before you do that, can you have the FDA folks that are on the line introduce themselves or at least say who they are.

MR. JEHN: We sure can.

DR. DAUM: I know you and Dr. Wilson are on.

DR. LEVIS: Hi. This is Robin Levis. I am the deputy director for the Division of Viral Products. I will be making a presentation on Jerry Weir's behalf because he is out of the office.

DR. DAUM: Welcome, Dr. Levis.

DR. LEVIS: Thank you.

DR. WILSON: Carolyn Wilson, associate director for research.

DR. PEDEN: Keith Peden, chief of the lab that you are reviewing today.

DR. DAUM: Welcome, Drs. Wilson and Peden.

DR. KRAUSE: This is Phil Krause. I am the acting deputy director of the Office of Vaccines, but I am stepping in for Marion Gruber who is out of town.

DR. DAUM: Thank you and welcome.

DR. MARKS: I did not start quickly enough. Sorry. It is Peter Marks. I am deputy director of CBER.

MR. JEHN: We have the big management here today.

DR. DAUM: I see that.

MR. JEHN: That is who is sitting at the table, Dr. Daum.

DR. DAUM: I cannot see so I have to take your word for it.

MR. JEHN: Next time we will have a camera. I promise.

DR. DAUM: I have actually done an NIH study section review with everybody on camera. It was kind of weird. It looked like Hollywood Squares.

I want to go back to my committee and ask them to now besides saying they are here just say who they are and

what their expertise is. Maybe we will start appropriately enough with Dr. Durbin and then -- everybody can speak up.

DR. DURBIN: Hi. This is Anna Durbin. I am at the Center for Immunization Research at Johns Hopkins Bloomberg School of Public Health. I am an internist infectious disease physician who specializes in clinical vaccine trials.

DR. DAUM: Very good. Who wants to go next? Dr. -- I know is not here. Dr. Gray is not here. Dr. Schoolnik.

DR. SCHOOLNIK: I am Gary Schoolnik. I am a professor of medicine, microbiology, and immunology at Stanford University.

DR. DAUM: Dr. Tacket is here.

DR. TACKET: I am professor at the University of Maryland, School of Medicine, Center for Vaccine Development. And my expertise is in early vaccine development.

DR. DAUM: Very good. Edgar, I know you are here.

DR. MARCUSE: I am Ed Marcuse. I am a professor of pediatrics and an adjunct professor of epidemiology at the University of Washington. I am based at Seattle Children's Hospital.

DR. DAUM: Dr. Air.

DR. AIR: Hi. I am professor of biochemistry at the University of Oklahoma Health Sciences Center in Oklahoma City. I work with -- antibody receptors.

DR. DAHM: Is Dr. Kester on the line?

DR. KESTER: Yes, I am. Kent Kester. I am a professor of medicine and associate dean for clinical research at Uniformed Services University, infectious disease, internal medicine, and clinical development of malaria vaccines.

DR. DAUM: Don, I think you said Dr. Hudgens is not joining us today.

MR. JEHN: That is correct.

DR. DAUM: Dr. Piedra.

DR. PIEDRA: I am professor in the Department of Molecular Biology and Microbiology and Pediatrics at Baylor College of Medicine. I am a pediatric infectious disease specialist by training. I do a lot of preclinical and clinical trials in respiratory virus vaccines and therapeutics.

DR. DAUM: Very good. Certainly not least, but last I guess is Dr. Tsai.

DR. TSAI: Hi. I work in the clinical development function within Novartis Vaccine. I am clinically trained as a pediatrician and also in public health epidemiology.

DR. DAUM: I am Robert Daum who is a pediatric infectious disease guy, University of Chicago, and I work on bacterial infections especially staphylococcal infections in children and adults.

That will do it with our introductions. We are going to review the laboratory of DNA viruses. We are going to review the report that is already done. Division of Viral Products and the OVRR today. Our first speaker is Dr. Carolyn Wilson who is the associate director for research at CBER. Her topic is different than the screen than it is in the program, but that is okay. It is applying regulatory science to advance development of innovative, safe and effective biologic products. Welcome Dr. Wilson and please go ahead.

Agenda Item: Topic I: Presentation of Laboratory of DNA Viruses, Division of Viral Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research

Agenda Item: Overview of Research/Site Visit Process

DR. WILSON: Thank you, Dr. Daum, and welcome to the committee. I am really just going to provide an overview about the center in general about our regulatory science programs and then also orient the committee to the

purpose of the site visit in relation to how we evaluate our programs and what your responsibilities are today.

On slide two, we regulate a variety of complex biologic products. Obviously, you are aware of the ones that are regulated in OVRR like vaccines and therapeutic probiotics and allergenic products. But in addition to those, we also regulate all the blood, blood components and derivatives, some related devices associated with maintaining blood safety, novel therapies such as cell and gene therapies, xenotransplantation products, certain human tissues, and also some devices related to cell therapies as well.

The complexity of the products that we regulate raise a number of scientific issues when it comes to trying to make regulatory decisions. In order for us to really be able to fulfill our regulatory mission, we feel it is critical to have a robust, regulatory science program to help address those gaps and knowledge that are required to make regulatory decisions.

For that reason, we developed a strategic plan for regulatory science. We have followed the major tenets that were published I think almost two years ago now in the CBER's overall strategic plan. I will not read through those because I will be going through them again in a few minutes. The links to the two plans are at the bottom of

the slide if anyone is really interested in getting more information about our thinking in these areas.

The vision for regulatory science and research is to be both proactive and anticipatory of regulatory and public health issues so that we can be responsive to emerging public health and regulatory issues. The science should be collaborative of the highest quality and relevance and as I mentioned earlier, integral to our regulatory mission and public health portfolio.

And importantly, it also provides the center with the scientific expertise, the tools, the data that we need to support our science-based decision making and policy development.

This graphic is really a way to just demonstrate how we apply regulatory science in the regulatory environment, how we apply our research. And really, everything starts with the public health issue that drives the development of a novel product. That novel product may generate certain challenges in a regulatory environment. Perhaps we do not fully understand the mechanism of action to be able to know what would be an appropriate potency assay. Maybe there is not a good preclinical model to assess the potential for efficacy or safety related to the product. That is where our in-house regulatory science program can address those gaps -- combination of discovery

science and targeted science to develop the new tools, data, methods, reference materials and so on that can inform our regulatory policy and decision making.

As we get better guidance out to sponsors as to what kind of data we need to support those decisions, we then also get better data submitted to us in regulatory submissions and then we are in a better position to make benefit/risk decisions and hopefully at the end of the day have a product that is licensed that is both safe and effective and has that positive impact on the public health.

Our research facilities include a core facility for a wide array of biotechnology. I will not read through the list, but I do want to highlight that we have recently been able to invest in Illumina sequencers and are very active in developing the bioinformatics infrastructure and analytics in order to evaluate those data. We also have some limited core support for flow cytometry, confocal microscopy and microarray.

We have a vivarium with procedure rooms to support work in rodents, non-human primates, and BSL-2 infectious agents, which is obviously of great importance for vaccines. And then we also have BSL-3 and animal BSL-3 laboratories.

Our center has a variety of scientific expertise represented. As you would expect, things like microbiology and immunology. In addition, we have various novel technologies that are being applied to our regulatory questions such as high resolution NMR, high resolution mass spec, multicolor flow cytometry, microarray, high throughput sequencing, and so on. And then other disciplines such as biochemistry, molecular biology, cell and developmental biology, epidemiology, and biostatistics. This creates a rich, interdisciplinary environment, which allows for good collaborations and cross talk between the various scientists.

Our researchers are what are called researcher-regulators. What this means is that they spend up to 50 percent of their time doing the same activities that full-time reviewers would do meaning that they not only review the same submissions that come in like INDs and BLAs and so on, but also they go out on inspections. They are involved in organizing and presenting at advisory committees, organizing and presenting workshops. They write guidance documents. Again, their data really does help to inform the policy in the center as well.

Because these research scientists are both members of the scientific community and so are going out and participating in relevant, professional and society

meetings hearing about the science before it even hits our doors. And then on the other side of their brain, they are actively engaged in the in-house review activities and can see across a whole platform of products to identify what might be the issues. It really allows us to really take that both proactive approach to be prepared for things that have not even come in-house yet, but we anticipate are likely to be hitting our doors while also being able to identify gaps that might move a whole class of products forward.

Obviously, we cannot do all this work by ourselves. We do extensive external collaborations with a number of academic government agencies, other institutions both within the US and internationally.

I wanted to spend a few minutes talking about how we review our research programs and how the site visit fits into the overall evaluation process. We have an annual review process where we have a research reporting database where we collect once a year updates on each project with regard to the progress from the prior air, their future plans, and their budget needs. And we also collect in that database all relevant scientific presentations, publications, other output that might be related to the program like guidance documents, employee invention reports, or patent applications.

And then that information is reviewed at a variety of levels. The lab chief reviews it, division director, the office ADR, which is Associate Director for Research and the office director. And they are looking at that information for the relevance to their stated priorities, the productivity of the program as well as the scientific quality. And then funds are allocated in accordance with those criteria.

The purpose of this process is really to both address an investigator initiated research model while still making sure that the research fits within our regulatory mission.

In addition to the annual review process, we also have two types of cyclic review every four years. The one that you are participating in or playing a role in is the external review by scientific experts in the field of which the laboratory is represented and that is what we call our site visits.

And then the report from those external site visits becomes part of a larger package that goes for an internal review by our Promotion, Conversion, and Evaluation Committee. That is where both decisions relating to conversion of staff to permanent status, obviously promotions and also just every four years even if an individual isn't up for a promotion or conversion and

evaluation for making sure that they are still working at the grade level to which they were assigned.

The site visit report that is generated by the site visit team is actually a draft report and it is distributed to the full advisory committee. That is the role that you have today as the advisory committee to review this report, make comments, make suggestions if necessary for changes, or if you agree with it as it is written, you can approve it in its current form. And then that becomes the final report once it is approved by the full advisory committee.

And then that report is really useful to the center and to the scientists. As I mentioned, it becomes a critical part of a larger package that goes for internal peer review. The PIs take the information and these reports very seriously as a way to improve their own research program. And management also takes the recommendations into account when making resource allocation decisions.

In the last few minutes, I am going to switch to the Office of Vaccines Research and Review with thanks to Konstantin Chumakov to just give an overview of their office. The mission of Office of Vaccines is to protect and enhance the public health by assuring the availability

of safe and effective vaccines, allergenic extracts, and other related products.

The activities that they engage in are to review, evaluate, and take appropriate actions on various regulatory submissions related to vaccines and related products including conducting inspections, developing policies and procedures, conducting research.

And then with regard to the research, the areas that are of high priority for this office are those that contribute to regulation of vaccines and related products by addressing scientific aspects of critical regulatory issues and also by having an in-house program that maintains a scientific base, which allows them to establish methods and standards to ensure continued safety, purity, potency, and effectiveness of vaccines and related products.

The research program also is an opportunity to recruit and maintain highly trained scientists who provide necessary expertise for the review process. And this expertise is also harnessed in leadership to the vaccine industry to facilitate development and introduction of new vaccines and related products.

The management process within the office and this is coming back to that slide I mentioned earlier, which refers to the annual review process. It really starts with

the principal investigator. Again, as I mentioned, there is this database where information is collected, but also principal investigators are -- they are submitting proposals to their lab chiefs to review. And those proposals are based on their own evaluation of what is going on in the field as well as the stated priorities provided by the office management. As I mentioned, that information is reviewed and discussed with the lab chief, the division director.

And then the division director generates what is called a division research portfolio. That is reviewed by a research management committee. The committee is composed not just of managers that are involved in research, but also managers that are involved in the regulatory full-time review process. It also includes a representation of PIs and full-time reviewers as well. It is a fairly crosscutting committee that can really see all of the different issues and also provides input into the priorities for that year. And based on the review by that committee then that informs development of the priorities and allocation of resources in accordance with those priorities.

And again, the rating of these projects is fairly similar to what I mentioned before. The public health significance is obviously a driving concern including

regulatory relevance. Scientific merit is obviously a critical component and the qualifications of the PI and productivity.

I just want to finish with a few comments about our move to the White Oak Campus because this has come up in some of the more recent site visits because as you probably know, we are moving in January 2014. The center will be starting to move. This is a photo of actually one of our labs that is fairly close to completion. You can see it is nice, new state-of-the-art facility. By design, we have built into this facility a capacity to really expand a lot of the work that we are doing that we really aren't able to do in our current restrictive footprint here at NIH and that includes an expanded vivarium with a new imaging facility, transgenic derivation space, expanded space for certain core technologies like flow, confocal, and sequencing.

We are going to go from three BSL-3 suites to ten BSL-3 suites, which allow us to work on a much broader array of infectious agents. Most of those suits have animal holding rooms. And we will have one suite dedicated to support sterile sorts and live cell confocal microscopy. Also BSL-2 and BSL-3 insectariums. This will allow us to expand our work on arthropod borne agents. Suites specifically designed to support microarray and PCR. A

very expanded NMR facility and dedicated mass spectrometry suites. We are excited that this is going to be an opportunity to really expand the infrastructure to help support high-quality science in the center.

I finally just will finish with a thank you to Anna Durbin and her site visit team for doing the review of this particular group and today to the advisory committee for your thoughtful engagement on the report. We look forward to your final recommendations.

DR. DAUM: We will ask question askers to identify themselves and ask clarifying questions for Dr. Wilson's presentation.

DR. KESTER: It is Kent Kester. Just a question with respect to your BSL-3 laboratory space. Do people there work on select agents or is this more just for safety purposes with non-select agents.

DR. WILSON: I think I am not supposed to disclose whether or not we work on select agents.

DR. KESTER: I understand.

DR. WILSON: Maybe I can say that we plan to pursue registration.

DR. KESTER: I understand. Thanks.

DR. DAUM: Anyone else? I have a couple of comments and questions. First of all, I am actually delighted. Some of you may know that this is my second

tour of chairing VRBPAC. During my first tour, the whole issue of whether CBER should be involved with research at all was a constant issue that we were dealing with. I am actually thrilled feeling very strongly that it is something they should be doing to see that we move beyond that. I do not think, Dr. Wilson, you even mentioned it. I think that is perfect.

My second comment is that members of VRBPAC who are on the line may not know that when this review begins, Mr. Jehn asked me who on the committee should be chosen to do the review. Dr. Durbin is unfortunately and her team are the recipients of my choosing them and then his asking them.

I wanted to tell the committee that their integrity and willingness to do this is crucial to the function of what we do. I know that sometimes people have said they are busy with this and busy with that and plus we all get busy. But I hope that you will regard these requests as coming from me and very important to the integrity of CBER, the research mission, and the functioning of VRBPAC.

Lastly, I have one more thing I would like to raise and then I would like to Dr. Wilson if she cares to comment on any of these things. You did not mention anything about the funding for research and I know that has

been an issue in the past with relationships between FDA and NIH and FDA and collaborators. I wonder if you could say something about it now.

DR. WILSON: Certainly, Dr. Daum. First, I want to just thank you for the comments that you made about the importance of the site visit and reinforcing the need to engage because we do really rely on this. It is a critical function for us. We really appreciate your recognition of that and support for that.

With regard to funding, actually the last three years including this year we have been very generously funded through the Medical Countermeasure Initiative, which is actually within the FDA, which was supported by a one-time supplemental source of funding in 2008 that went to DHHS that Congress actually redirected to the FDA for supporting medical countermeasure development.

This has been terrific. It has brought in many millions of dollars into the center to help increase both infrastructure as well as support directed programs that were relevant to that area. Unfortunately, that one-time supplemental funding -- this is our last year with that. Funding will become a challenge. As you know, there is a sequester and that is a challenge. And the next year we are moving to White Oak and that will be additional

expenses. It is something that we are trying to manage, but it will be challenging in the current environment.

DR. DAUM: Very good. Are there committee questions or comments? In their absence, I am going to think Dr. Wilson very much for the site review. I certainly appreciate it. I am sure committee members did too. And move on to ask Dr. Levis, who I know is on the line, to give us her overview of the Division of Viral Products of where we are.

MR. JEHN: Dr. Daum, before Dr. Levis resumes, I just wanted to add for the record Dr. Konstantin Chumakov is at the table now. And also just to make sure that everybody is able, who is connected and will be connect can see the slides advancing. Has everybody been able to see that? Great. Thank you. One member commented that he could not see it. It must be a problem with his version on the computer. Sorry for the interruption.

Agenda Item: Overview of Division of Viral Products (OVRR)

DR. LEVIS: That is okay. Thank you for giving me the opportunity to speak. Again, I am here on Jerry's behalf, Jerry Weir, who is the director of the Division of Viral Products. I am going to continue the introduction and bring it down a level from Carolyn's introduction to

just a give a general overview of the Division of Viral Products and how and why and what we do in the division.

My first slide is just an overview of the division we have in immediate office with Jerry and I as the director and deputy director and support staff in that office related to the regulatory work that goes on in the division and just general personnel support.

And then the division is made up of seven laboratory units, each with a chief or acting chief. These laboratory units are based very broadly on product areas, regulatory product areas, and we establish the laboratories based on the scientific expertise that we need or would like to support the regulatory mission that we mission. Today, highlighted in blue, you will see we will be discussing the Laboratory of DNA Viruses with Keith Peden as the chief.

The Division of Viral Products basic mission statement and the functions we find are critical for us to perform are to regulate viral vaccines and related biological products, ensuring their safety and efficacy for human use. Along with the regulatory point of view, we also work to facilitate the development, evaluation, and licensure of new viral vaccines that positively impact the public health. That is done in conjunction with our industry counterparts as well as our researchers.

The Division of Viral Products. Our major responsibilities from a regulatory point of view are to work on investigation new drug and biological license applications and other pre-marketing activities. BLA supplement review, those are the review of changes to already licensed products. Lot release review and other post-marketing activities including GMP inspections and following up on biological product deviations.

We also have quite an extensive involvement in consultation with other public health agencies including the World Health Organization, CDC, NIBSC, and other global national regulatory authorities where we have expertise that can contribute to ongoing activities of those agencies.

The last bullet, which is most critical for today's discussion, is the research going on in the division related to the development, manufacturing, evaluation, and testing of viral vaccines.

The role of research in the Division of Viral Products is that we have research and laboratory activities, which complement our regulatory mission. I think we have done a good job over the recent years of evolving our research program to do just that. We address issues related to regulated viral vaccines. And in addition, we put effort into anticipating and addressing

issues related to the development and evaluation of new viral vaccine products. This can be through general issues applicable to all products or product classes such as cell substrate issues, improved test methodologies, reagent development, but also very specific product issues for any one vaccine such as the determination or analysis of correlates of protection, animal models necessary for the animal rule implementation, and other product-specific issues.

Just to give a little bit of the staff and personnel issues. The Division of Viral Products over the last 12 years as shown on this slide has ranged from 65 up to 80 full-time FTEs. Those are full-time government employees with an average between 75 and 80. Highlighted on this slide is CT for counterterrorism and FLU and those are points where some funding and specific initiatives came to the center where personnel were hired to address very specific issues. But in general, we have approximately 75 to 80 FTEs in the division divided amongst the labs. And shown in this slide is actually the breakdown by laboratory. Important for today's discussion is the DNA virus lab and you see it is the largest lab in the division.

And to address the issue of budget with respect to the Division of Viral Products, the blue bars are the

internal funding received directly through CBER and also external funding. You can see over the last 12 years with a few dips here and there our external funding the researchers in the division have been very successful at getting external funds were available to us to help support our research mission.

And the internal funding shown in blue you can see as Carolyn highlighted in the last years the very large numbers are reflective of this MCM money that was made available to us. My guess is next year's bar is going to be significantly decreased in the blue funding arena. The Y-axis is millions of dollars.

With respect to other site visit evaluation that was here today it is to look at our program review. The assessment of progress on projects pursued since the previous site visit. The individual review for certain individuals within the lab and also the evaluation of future directions. This site visit evaluation protocol is the same for all laboratory units within the division. I thank you very much for your consideration with respect to the review today.

DR. DAUM: That was very helpful and wonderful and thank you. There is an opportunity for committee members to ask Dr. Levis clarifying questions about her presentation if there are any.

DR. PIEDRA: I have one question. This is Tony Piedra. I would like to ask if Dr. Levis thinks that the level of funding is sufficient to conduct all that they are required to do.

DR. LEVIS: I will say over the last three years the funding has allowed us to very nicely conduct very robust programs and in fact take advantage of some of the additional funding to build the infrastructure with respect to some very specialized equipment. We are getting new electron microscopes state of the art. We have greatly expanded the confocal microscope much of this with the eye of the move towards White Oak where we really want to have things in place as Carolyn said to really continue and expand the research program.

I think we are all a little nervous about what the next couple of years is going to look like with respect to that. We have been lucky to have this opportunity to really upgrade and modernize many of the research facilities and equipment, big-ticket equipment, i.e. the electron microscope. Our current electron microscope is almost 20 years old. To really have the opportunity to get a new one that will be delivered to White Oak ready for use is really nice. It gets a lot of use. That is an important thing. Yes, people are very nervous from this

date forward. Right now people are pretty happy with the way things have been over the last three or four years.

DR. DAUM: Other committee questions or comments, please -- to hear any, I will thank Dr. Levis very much for filling in for Dr. Weir. Tall shoes. You did a great job. Thank you. We will call on Dr. Peden next to talk about the Laboratory of DNA Viruses itself and give us his comments.

Agenda Item: Overview of the Laboratory of DNA Viruses

DR. PEDEN: Thank you very much. I will say thank you very much Dr. Durbin for being chair of our site visit committee and I hope by saying that you have written a good report.

This is the organization on the next slide of the Lab of DNA Viruses. There are four PIs in the group: Phil Krause, Andrew Lewis, Jerry Weir, and myself. And the names of the units are listed on this slide. And the personnel on each of these units are listed underneath.

I just want to comment on some of the changes that occurred in the LDNAV since the last site visit in 2008. One principal investigator, Mike Merchlinsky, left in late 2008 for greener pastures and probably a few more green backs. Andrew Lewis stepped down as chief of the lab, but retains his position as principal investigator. I

transferred to LDNAV in 2010 and was appointed chief in 2011.

Dr. Weir continues to be principal investigator in the lab with his other duties extensive as they are, director of DVP and acting chief of the Lab of Pediatric Respiratory Viral Diseases. Dr. Phil Krause continues to be PI in this lab as well as being acting deputy director of the Office of Vaccines Research and Review. As you can see, it is a rather a strange structure in the lab since I am in charge of people who are really in charge of me. But I think it works pretty well because if you are rational and mature adults then I think it works okay.

DR. DAUM: Probably we won't comment any further on that issue.

DR. PEDEN: What I would like to do now is just say how our public health mission is helped by our research programs. And the 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.

In addition, our research helps to resolve the inevitable vaccine health crises that arise. The most recent was the finding in 2010 by an academic lab that a porcine circovirus contaminated a rotavirus vaccine. And because of the talented scientists in his group, Dr. Krause

was able to provide data very rapidly to the VRBPAC that convinced them that there were no safety concerns raised by the finding. It was only because we have an in-house research program that this could have happened. I commend Dr. Krause and his group for doing this.

In addition, Dr. Weir is involved in developing reagents and assays to assist sponsors in pandemic preparedness for potential pandemic influenza, such as those caused by H5N1, H1N1, and now the one that is potentially is very concerning is the H7N9.

On the cell substrate issue, Dr. Andrew Lewis has programs to assess whether the quantitative tumorigenicity assays can assist in cell-substrate characterization. In addition, he has now moved on to investigate whether microRNA profiling of cell substrates can be used as a surrogate for tumorigenicity assays.

In my group, we are addressing also cell-substrate safety issues. We have had a longstanding program on cell-substrate DNA issues. And more recently, we are trying to address whether understanding the mechanism whereby a cell becomes tumorigenetic assist in eliminating risks associated with using such cells for vaccine manufacturer. This was a subject of the VRBPAC in September last year.

Now, what I want to do is just summarize some of the research programs in a bit more detail of all the PIs. The first one is Dr. Weir and the Unit on Viral Gene Expression. The goal of the research effort in his group is to facilitate the development and licensure of vaccines for high-priority viral diseases by addressing issues important for product evaluation, and to facilitate the development and evaluation of new-generation smallpox vaccines. Another part of his program is to facilitate the development and evaluation of pandemic influenza vaccines.

With respect to the smallpox vaccines, this is a long-standing interest with Dr. Weir and was a collaboration for many years with Mike Merchlinsky until he left in 2008. The current smallpox vaccines have certain side effects, as everyone knows, some of which can be serious; therefore, new vaccines are being developed.

Current and future focus of research efforts include comparative immunogenicity of the new-generation smallpox vaccines, for example, modified vaccinia Ankara and LC16m8 with the licensed smallpox vaccine, ACAM2000.

They are trying to identify biomarkers for vaccine effectiveness because there is no correlative of protection for smallpox vaccines. And they are developing assays for product characterization and pre-clinical and clinical efficacy evaluation.

The assays they are trying to develop are alternatives really to the traditional plaque reduction neutralization test. This has been used in the efficacy evaluation of ACAM2000. However, as everyone who has done these assays know, it is laborious and time consuming. It requires large quantities of various sera. A single standardized assay cannot be used to assay candidate new-generation smallpox vaccines. And viruses used for neutralization has an effect on measured neutralization titers.

There are exploring the possibility of using alternative neutralization methods, for example, viruses expressing marker genes. This should result in higher throughput assays and an assay restricted to the strain used -- the problem is it was assay restricted to the strain used to construct recombinant.

Another effort is to develop a rapid neutralization assay, which can be miniaturized to reduce sample requirements, and capable of measuring neutralization of multiple viruses under identical conditions. In our group, Haru Murata has been advising one of Dr. Weir's people to develop an assay that we have had some considerable experience with, which is a qPCR-based microneutralization assay.

On the side of the pandemic influenza vaccines, pandemic influenza preparedness is an extremely high public health priority and particularly true for the FDA. Jerry's lab has obtained support from supplemental pandemic influenza from HHS/FDA and directly through the Biomedical Advanced Research and Development Authority or BARDA.

The current and future focus of research efforts include development of alternative approaches and improved methods to expedite the production and calibration of influenza vaccine reagents, to develop and evaluate new methods for potency determination of influenza vaccines, and develop research tools to better understand the nature of the protective immunity to pandemic influenza.

In particular, those people who are experts in influenza vaccine field, the SRID, Single Radial Immunodiffusion Assay, is not a particularly sensitive assay and it is rather antiquated and is really not that good. Dr. Weir's lab is trying to develop more rapid pandemic influenza response potency assays.

However, if you want to replace a current assay, multiple criteria must be met to replace this. Therefore, it has to be accurate and precise and equal to or greater than current SRID. The dynamic range of the assay needs to be equal to or greater than the current SRID, which should

not be that difficult since the assay has a very limited dynamic range.

The potency measured should correlate with the current SRID results to convince people that these assays in fact can be used. Alternatively, it could correlate directly with clinical benefit. They should be capable of measuring potency of vaccine strain subtypes in a trivalent and now as we know a multivalent vaccine that are coming down. Stability indicating, otherwise, they should be capable of quantifying sub-potent vaccines and transferable and practical. This is the nature of the outline of Jerry's research.

I will now turn to the Unit of Viral Latency with Phil Krause as the senior investigator. Phil's research is essentially divided into two sections. The detection of latent or persistent viral infections. This is important for cell substrates and adventitious-agent issues. But it is also important to understand disease pathogenesis.

And also, it is determining strategies of viruses used to become latent and subsequently reactivate to understand how this affects disease caused by viruses. This is important for understanding what vaccines must accomplish to protect against viruses that have a latent state. It is important for better understanding of live-attenuated vaccines that can establish latency. And it is

also important for understanding latency in the context of cell substrates.

Phil's lab has worked out a non-specific virus detection system. The nuclear acid extraction can be optional capsid or particle enrichment. And they use a non-specific PCR, which they have termed degenerate oligonucleotide-PCR or DOP-PCR in most of their experiments.

In addition, they have applied massively parallel sequencing on next-gen sequencing. Very impressively for me anyway they have developed algorithms in their own lab to establish in the group to analyze the data.

With respect to sample preparation, Phil's lab has shown that capsid enrichment can improve the sensitivity of virus detection. They have caveats that they do not remove all the new cell nucleic acid. And the assay does add some variability and may concentrate ribosomes and ribosome-associated RNAs.

However, viruses from many classes and families have been detected by the DOP-PCR method and these include many DNA viruses and RNA viruses. And in the CD that you have, Phil's presentation, there is a whole list of viruses that the lab has managed to detect.

In addition, Phil's lab in just the last couple of years or so embarked on another way to find adventitious

agents or the history thereof. This is a messenger RNA Display, which they used to identify epitopes. It is a powerful method for mapping linear peptide sequences bound by an antibody. It has claimed to be more than three logs more powerful than the phage display.

It is potentially useful in diagnosis of infections if you are looking for antibodies that are present in sera that have been exposed to an agent, understanding immune responses, characterization of monoclonal antibodies, and identifying immunogens. They have adapted this method to use massive parallel sequencing. This helps their analysis in using this method.

In addition, Phil's lab has been interested for many, many years -- I should not say many, many years, but many years on HSV latency and reoccurrence. As we know, HSV preferentially establishes latency in certain neuronal cell subtypes. Latency occurs when lytic genes are inhibited. And virus replication and likely viral spread and reactivation occur when lytic genes are expressed. The outcome of infection in any given neuron represents a contest between the forces that promote replication and those that promote latency, good versus evil.

In addition, they found that the LAT is involved with establishing and maintaining the latent state. And

importantly, Phil's lab was the first to identify microRNAs that appeared to be involved with latency and encoded by the LAT transcript.

Now, I will move on to the cell substrate, two units. I will sort of on myself first, not because that is the way I think, but because some of what I say in background will be relevant for Andrew Lewis' project. This is our unit and overall research objectives. To identify the potential risks associated with the use of novel cell substrates, particularly tumorigenic cells or cells derived from human tumors.

We tried to develop quantitative assays to measure risk factors and determine whether the risk factors can be mitigated, in other words, for testing, removal during manufacturing, et cetera. As I have said, this has been a sustained collaboration with Andrew Lewis over the last 15 years or so.

The current projects. What we have in the unit is development of animal models to assess oncogenicity of cell-substrate DNA. They are the people involved in those projects. Development of in vitro assays to quantify the degree of reduction of the biological activity of DNA. And to determine whether identifying the mechanism of neoplastic transformation can assist in estimating the risk of using such cells for vaccine manufacture. These could

be genetic mechanisms or epigenetic mechanisms. We really started to probe the epigenetic side of this because our own view is that some of these spontaneously transform cells are transformed probably through epigenetic mechanisms.

The general approach we take for this is define risk approach. This was something that was presented to the community that Andrew Lewis, Phil Krause, and I were involved in 2000. It is to identify the risk factors, develop quantitative assays to measure the risks, generate data to determine the probability of a risk event occurring, and use these quantitative assays to determine ways these risk factors can be reduced and to quantify by how much.

The question of DNA has been a question that has been unanswered for about 50 years. Our studies have involved both the infectious activity and the oncogenic activity of DNA.

I have just summarized some of the research outcomes on DNA on the oncogenicity side. In vivo assays have been developed that can detect the oncogenic activity of cellular oncogenes. We have shown that and published that. Several rodents have been identified that can detect oncogenic activity of our ras/myc plasmid. This is Hawley rat plasmid and C-myc plasmid. When you put these two

genes on the same plasma, you can detect tumors at 1 nanogram or lower. The more sensitive rodents we have found are newborns or CD3 epsilon, newborns of SCID and newborns of the p53 mutant mouse and recently the newborn rats. Some of these data were presented at the VRBPAC last year.

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.

However, there are reservations with these types of assays that we are coming to believe. It is unlikely to detect the oncogenic activity of an activated dominant oncogene in cellular DNA due to the dilution effect. The plasma DNA is about a million fold less complex than of a mammalian cell. Therefore, an oncogene you can detect and say 1 nanogram. You would need about a million fold more DNA to detect that and that is not possible to put into rodents in general. And even if this is possible, only a subset of dominant oncogene score positive in this assay. We know the ras family score positive and the myc do not.

We also know that the HPV oncogenes E6 and E7 do not score positive. There are probably a whole lot of oncogenes, cellular oncogenes activated that do not score a positive in this. Our approach is probably coming around to the feeling that it may be best to limit the amount and

size of residual DNA in vaccines and not to rely on these in vivo oncogenic assays.

Andrew Lewis' unit of adventitious agent and cell substrate. Major questions addressed by his tumorigenicity research are can quantitative tumorigenicity assays assist in identifying risks from cell substrates. What are the mechanisms of spontaneous transformation? Are there risks from the use of immortalized cells for vaccine manufacture? How do immortalized cells evolve to become tumorigenic? Does this fact represent a risk?

On Project 1, understanding the evolution of non-tumorigenic to tumorigenic VERO cells. VERO cells, as most people know, are the most widely used cell substrate for vaccine manufacturing. VERO cells can evolve from a non-tumorigenic to a tumorigenic phenotype by passage in culture.

In the VRBPAC in 2000 suggested that DVP undertake a research program to determine whether the capacity to become tumorigenic itself represented a risk factor. In other words, I understand the mechanism of neoplastic transformation in VERO cells. At the time, we thought this was a recommendation and a project that was way beyond the scope of most humans. It turns out that it was rather perspicacious on their part and we have done

some work on this. We are, in fact, generating data to understand the mechanism of how this happens.

And part of that is a project to look at the microRNA profiles of VERO cells as they move from non-tumorigenic to tumorigenic. And we have documented those patterns. We have identified microRNAs whose expression correlates with the acquisition of a tumorigenic phenotype. Current work is determined how general this is and whether we can use the expression of microRNAs as biomarkers for a tumorigenic phenotype in VERO cells.

In addition, Andrew Lewis has a project on Madin-Darby canine kidney cells. MDCK cells are widely used in influenza virus research and have been used for manufacturing of an inactivated influenza vaccine. The US license was given in late 2012.

Because of the unusual properties of MDCK cells, there are tumorigenicity properties, their induction of a failure to thrive syndrome, MDCK cells have raised safety concerns. The idea is to determine the cause of this aberrant dose-response relationship of certain MDCK cell lines, determine the biological basis for failure-to-thrive syndrome, and to determine the mechanism of transformation of MDCK cells.

The outcome of the research that we have done on the MDCK cells, we can conclude that the tumorigenic

phenotype of MDCK cells is complex. Understanding the pathophysiology of the failure-to-thrive syndrome and the processes involved in the development of subpopulations capable of forming different types of tumors to contribute to the management of MDCK cells as reagents for vaccine development.

And understanding the processes of neoplastic transformation of MDCK cells is complicated by the lack of earlier passages. Because we do not have a day one MDCK, Andrew's lab has created new dog kidney lines from the canine kidney that we obtained from the NIH that they had to sacrifice and with passages available from the primary kidney cells to immortalized cells to tumorigenic cells. This should help us in understanding what events occur in the immortalization of dog kidney cells. They should be directly extrapolatable to MDCK cells. We do have, in fact, preliminary data in collaboration with Matthew Breen's lab in North Carolina. In fact, there are many genetic rearrangements that occur in MDCK cells also occur in our dog line. This seems that this may well be true. There are constant changes in dog canine kidney cells as they move immortalized to tumorigenic.

In addition, Andrew's lab has been developing neutralization assays. This is really in collaboration with us and with Haru Murata. It is based on earlier work

establishing a neutralization assay for SV40 using a qPCR endpoint.

We have adapted the assay to RNA viruses now using a qRT-PCR endpoint. The influenza virus qRT-PCR-based microneutralization assay has just been published in PLOS One. The respiratory syncytial virus qRT-PCR-based microneutralization assay, which we are doing in collaboration with Judy Beeler, we just submitted for publication. And we are currently working on establishing an analogous assay for human metapneumovirus. These respiratory viruses are actually rather important in the population.

These assays are highly adaptable to high throughput and robotics since no nuclear acid extraction is required. These assays we think are very useful and they are highly sensitive and highly robust and adaptable as you can see to many different viruses. Of course, Jerry's lab is doing it with vaccinium.

I think that is the review of the lab and I thank you for your attention.

DR. DAUM: And we thank you very much, Dr. Peden, for that rather amazing download of information in a short time. Clarification questions for Dr. Peden. Thank you very much for your excellent presentation. Before we move on to the open public hearing, ask any of the FDA personnel

to tell us what happens. We had a little glimpse of it from Dr. Peden's presentation. What happens to the recommendations we make today in terms of next?

DR. WILSON: The report is used as part of a package for those individuals and we won't discuss the specifics here in open session, but in closed session, we can discuss the individuals that are being requested in terms of recommendations for conversion or promotion. Those packages would either go forward or not to an internal peer review committee for those personnel actions depending on the recommendations of this committee that are within the report.

And then also as I mention, management will use the recommendations generally in terms of resource reallocations or other management decisions in terms of the laboratories and then the PIs will certainly take to heart a lot of the scientific direction -- recommendations about scientific directions is always very welcomed and thought about very carefully by the investigators. Is that what you were asking, Dr. Daum, or did I not answer your questions?

DR. DAUM: You have answered it perfectly.

DR. CHUMAKOV: This is Konstantin Chumakov. In some cases when there is a criticism in the report, we also ask principal investigators involved to provide us some

comments and provide us a plan to correct the issue. And if necessary have follow-up meetings in a few months or maybe a year just to see whether the program gets back on track.

DR. WILSON: Right. And actually I should have mentioned that we also just recently revised our site visit SOP to incorporate a requirement for the office management to provide in writing a response to the recommendations from every site visit report that comes to me and the center director for review and consideration so that we can make sure that the recommendations are being considered and what actions are being taken in response to those recommendations.

DR. DAUM: To share a report like that would be review committee or with VRBPAC as a whole?

DR. WILSON: The report is going to be an internal report. It would be up to the discretion of the division and office management whether it would go forward as a part of the site visit package the next time that unit comes up for review.

DR. DAUM: If I can have my two cents, there is nothing like feedback. As a reviewer and as a VRBPAC committee member I would love to have any and all you care to share.

DR. WILSON: Thank you. I appreciate that.

DR. DAUM: Any other comments from committee about this process before we move on to the next phase. That having been done and there be no further comments, I guess I would ask whether there is anyone who wishes to participate -- of this meeting.

MR. JEHN: We have no one present who wishes to speak in open public hearing. With that said, just take a moment to clear the room of those who will not be involved in a closed session. I will let you know when. It should just be a moment.

DR. DAUM: Four-minute break.

MR. JEHN: Yes. Maybe a two-minute break.

DR. DAUM: I have 10:06 central so everybody can adjust to their own time zone. We will reassemble at ten past the hour.

(Whereupon, the open session concluded.)