Food and Drug Administration
Center for Biological Evaluation and Research (CBER)

141st Vaccines and Related Biological Products Advisory Committee

January 14, 2016

Office of Vaccines Research and Review (OVRR)
Division of Viral Products (DVP)
Laboratory of Method Development (LMD)
Building 31, Great Room, Salon A
Silver Spring, Maryland

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

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PROCEEDINGS

Agenda Item: Call to Order and Opening Remarks, Robert Daum, M.D.

DR. DAUM: Let me just begin by calling the meeting to order, and turn the floor over to Dr. Vijh, who will read the conflict of interest statement.

DR. VIJH: Thank you, Dr. Daum.

Good day, everyone. I am Sujata Vijh, the Designated Federal Officer for today's meeting of Vaccines and Related Biological Products Advisory Committee. Ms. Denise Royster is the Committee Management Specialist for VRBPAC. On behalf of the FDA and the Center for Biologics Evaluation and Research, we would like to welcome everyone to the 141st VRBPAC meeting described in the Federal Register notice of November 27, 2015.

As you all know, members are participating via phone today, and the meeting is also being webcast live. Before proceeding to administrating remarks and reading the COI statement, I would like to make a quick roll call of the members on the phone for the official record.

As you know, Dr. Robert Daum is the chair of VRBPAC. So I am going to follow the roster and quickly do a roll call. Dr. Daum?

DR. DAUM: Dr. Vijh, we could introduce ourselves

while you are calling out the names.

DR. VIJH: That's a good idea, Dr. Daum.

DR. DAUM: I'm pediatric ID at the University of Chicago.

DR. VIJH: Thank you. Dr. Hudgens?

DR. HUDGENS: Michael Hudgens, professor of biostatistics, University of North Carolina.

DR. VIJH: Dr. Piedra?

DR. PIEDRA: Here. Professor in the Department of Molecular Virology and Microbiology and Pediatrics at Baylor College of Medicine.

DR. VIJH: Dr. Ruth Lynfield?

DR. LYNFIELD: State epidemiologist and medical director at the Minnesota Department of Health.

DR. VIJH: Dr. Janet Englund?

DR. ENGLUND: I am here. Professor in the Department of Pediatrics at the University of Washington and Seattle Children's Hospital.

DR. VIJH: Dr. Karen Kotloff?

DR. KOTLOFF: Professor of Pediatrics and Pediatric Infectious Disease at the University of Maryland School of Medicine.

DR. VIJH: Dr. Sarah Long?

DR. LONG: Professor of Pediatrics Drexel

University College of Medicine and Chief of Infectious Diseases at St. Christopher's Hospital for Children in Philadelphia.

DR. VIJH: Dr. Patrick Moore?

DR. MOORE: Hi, Professor of Microbiology and Molecular Genetics here at the University of Pittsburgh Cancer Institute.

DR. VIJH: Dr. Moore, you are very soft. So maybe when you speak the next time, you could be a little bit louder.

Dr. Mark Sawyer?

DR. SAWYER: Professor of Pediatrics at the University of California San Diego, Pediatric Infectious Disease specialist, and I'm at Rady Children's Hospital San Diego.

DR. VIJH: Dr. Edwards? Kathryn Edwards? Dr. Kathryn Edwards, could you please unmute your line?

DR. EDWARDS: (No response.)

DR. VIJH: Dr. Filip Dubovsky?

DR. DUBOVSKY: I am an Industry Representative from AstraZeneca, Pediatric Infectious Disease specialist.

DR. VIJH: Thank you. Your line wasn't too clear. So we will watch out for that.

Dr. Vicky Pebsworth?

DR. PEBSWORTH: Yes, hi. I'm the Consumer Representative from the National Vaccine Information Center. I am the Director of Research and Patient Safety.

DR. VIJH: Dr. Kathryn Edwards, can you hear me? Okay, so you can't talk, but you are on the phone and you can listen to us. Please send me an email if that is the way it is so we won't bother you too much.

So what I would like to do is go through the meeting format quickly. We will begin today's meeting with a session that is open to the public, followed by open public hearing, both of which are available via live webcast. If there are no comments from the public, the meeting will go to the closed session that will not be webcast.

For the closed session, FDA staff being evaluated will leave the room, and the alternative industry representative, Dr. Filip Dubovsky will also leave the phone call.

As you heard, Dr. Vicky Pebsworth is a temporary voting Consumer Representative for this meeting, and we have Mr. John Bowers who is a transcriptionist and sitting in the room with us.

What I would like to do is now have FDA staff seated at the table introduce themselves. We would like to

begin the introductions with Dr. Wilson.

DR. WILSON: Carolyn Wilson, Associate Director for Research Center for Biologics.

DR. GRUBER: Marion Gruber, Director, Office of Vaccines, for FDA CBER.

DR. WEIR: Jerry Weir. I'm the Director of the Division of Viral Products at CBER.

DR. RUBIN: Steven Rubin. I'm the acting chief of the Laboratory of Methods Development in the Division of Viral Products.

DR. CHUMAKOV: I am Konstantin Chumakov. I serve as Associate Director for Research at the Office of Vaccines, and I also am a Principal Investigator in the Lab of Method Development that is being reviewed today.

Agenda Item: Conflict of Interest Statement, Sujata Vijh, Ph.D. DFO

DR. VIJH: Thank you all. I would like to request everyone please check your cell phones to make sure that they are turned off or in silent mode. Also request members on the phone and audience in the room, please state your name and speak clearly and loudly into the microphone or phone so that the transcriber can hear you.

I would now like to read the COI statement for the public record.

The Food and Drug Administration is convening today's meeting of the 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 or regular federal employees from other agencies that are subject to the federal conflict of interest laws or regulations.

The following information on the status of this advisory committee's compliance with federal conflict of interest laws, including but not limited to 18 U.S. Code Section 208 in the Federal Food, Drug, and Cosmetic Act, is being provided to the 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 Method Development, Division of Viral Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research. This overview is a nonparticular matter. Based on the agenda, it has been determined that this overview presents no actual or appearance of a conflict of interest.

In closed session, the committee will review and discuss the report from the FDA site visit. Dr. Filip Dubovsky is serving as the alternate industry representative, acting on behalf of all related industry. He is employed by MedImmune, Inc. Industry representatives are not special government employees and do not vote.

The conflict of interest statement will be available for review at the registration table. We would like to remind members, consultants, participants, that if discussions involve any products or firms not in the agenda for which the FDA has a personal or imputed financial interest, the participant needs to exclude themselves from such involvement, and exclusion will be noted for the record.

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

Thank you, and I hand over the meeting to Dr. Daum.

DR. DAUM: Thank you very much, Dr. Vijh.

Before I begin, I would like to thank Dr. Pedro Piedra and Dr. Janet Englund for their hard work in preparing what we are about to hear in terms of a review.

I have done it myself, and I know what is involved, and I appreciate it.

We have four talks from FDA before we begin our deliberations. I can assure you that none of the people who are about to speak have ever given this talk before, and it's brand-new.

So Dr. Wilson, we will call on you first to give an overview of CBER research and the site visit process.

Agenda Item: Overview of CBER Research/Site Visit Process, Carolyn Wilson, Ph.D., Associate Director for Research, CBER, FDA

DR. WILSON: I am at the podium. I just want to make sure that people on the phone can still hear me all right. Thank you, Dr. Daum. As you know, unfortunately you have heard this talk a million times. So I apologize to you in particular, and hopefully there are enough new people on the committee that it will still be fresh to them. I have a couple of new slides maybe to keep you awake.

I also want to thank the cochairs, Drs. Piedra and Englund, for their work on this site visit. It is a lot of work, and we really do appreciate the time that goes into the review and the recommendations.

So on the next slide, so I just want to start

with a quick overview of the strategic plan for regulatory science. It is centered around six major strategic goals that are actually in the CBER strategic plan, focusing on increasing national preparedness, improving global public health, and enhancing the ability of science and technology to facilitate safe and effective development of biological products and ensuring safety, in this case referring really to post-marketing evaluation of biological products and advancing regulatory science and research and managing for organizational excellence.

We address these goals by looking at regulatory science or the research in our center as a part of really the life cycle of product development and playing an important role to facilitate product development. It really starts with a public health problem that drives the development of a new product. This leads to potential regulatory challenges, depending on how evolved the science is around that product. Maybe there is not a good preclinical model. Maybe there is not a good understanding of the mechanism of the product to be able to develop a potency assay. Perhaps reference materials are needed in order to evaluate product quality.

It's these kinds of gaps in the scientific knowledge or understanding of these products that really

drive the scientific portfolio of our regulatory science program, and it's through a combination of discovery and targeted development of new tools that we then are in a better position to create the knowledge and the tools to support regulatory policy and decision-making.

As we go forth with better policy, that's better guidance to sponsors, and then they are in a better position to provide data to facilitate our evaluation of the benefits and the risk so that at the end of the day, we hope that there is a licensed product that is both safe and effective and having a positive impact on that public health problem.

Then, of course, it doesn't stop there, but there is also a post-marketing surveillance for potential safety events associated with that licensed product that continues.

So in the Center for Biologics, our researchers are actually what we call researcher regulators, and what this means is that these staff not only run or perform research, but they also perform all the review activities of a fulltime reviewer, meaning not only reviewing submissions, but also going out on inspections, writing guidance documents, organizing advisory committees, workshops, and so on.

So because these scientists are both active scientists in their own field going out to meetings in their own discipline and hearing cutting edge developments in their fields and at the same time reviewing and seeing what is coming into the agency, this allows them to be perfectly poised to be able to in an investigator-initiated way identify where are the gaps in knowledge, both proactively and as products come into the agency.

This, we think, allows for us to have a very relevant and useful regulatory science program. We also do this through a variety of external collaborations. The next few graphs are just data that we pulled from the FY15 CBER research reporting database. This is a map of the United States showing collaborators across the country, a map showing that we also collaborate globally, and then finally this pie graph shows that we collaborate with a wide variety of sectors.

We look at our research on an annual basis through an online research reporting database where PIs provide progress reports, future plans, budget needs. We collect presentations, publications, other relevant output. For example, is there an employee invention report or other tech transfer related things such as a patent application?

It's then reviewed by a number of levels, lab

chief, division office, associate director for research and office director, and it's looked at for the relevance to stated priority areas, productivity of the program, the quality, and feasibility of the studies, and then funding is then allocated according to those evaluations.

In addition to that annual review, there is a cyclic peer review of every PI every four years, and this is the component that we are really dealing with today, which is the external peer review, which we call site visits, that is done by a panel of scientific experts in the relevant areas.

The output of that review is the report that you are going to be talking about in closed session, and that becomes part of a much larger package that goes to an internal peer review committee called the Promotion and Conversion Evaluation Committee. This report, which you are reviewing today, is developed as a draft report by the site visit team and comes to the full advisory committee. It is your purview to either approve it today or you can approve it with modifications or you can send it back to the site visit team.

But once it is approved by the full advisory committee, then it is used in a variety of ways. It is used, as I mentioned, by the PCE as part of their package

for personnel actions. The PIs take the recommendations in these reports very seriously in looking at how to improve their own research program, and then of course management looks at them when it comes to resource allocation decisions.

I wanted to just mention something new in the center we just launched actually just this month, which is a CBER peer mentoring group. I know this is an issue that has come up in prior discussions with this committee and elsewhere, whether or not CBER has a mentoring program, and so what we have done is we have done a lot of looking at other programs, for example at NIH and academic institutions, and trying to understand how we can develop a peer mentoring program within the center, which is fairly small and has fairly thin expertise in the sense that we have diverse expertise, but sometimes that expertise is an n of 1.

So what we decided is that rather than trying to match people up one on one that we have a monthly meeting, which would be open to all PIs. We have one senior PI, who will be rotating. We have a group of about six volunteers who will rotate. So a different PI will be there each month, and they will just be available for other PIs to answer general issues about how to manage their labs,

recruitment, budget, personnel issues, and other types of mentoring that could be useful.

The other thing I wanted to mention, since we last met I believe we have moved to the White Oak campus, and so this is a picture of the outside of our new Life Sciences-Biodefense laboratory. It's located in what's called the Southeast Quad. We have been here since summer of 2014, and these are a few shots of -- on the upper right-hand quadrant, a break area for people to eat lunch, and then the bottom two pictures are typical BSL-2 laboratories.

The new lab facility gives us a state of the art vivarium, with an MRI, digital x-ray, in vitro imaging system, ultrasound, transgenic derivation facility. We have expanded space to support core technologies of flow cytometry, confocal, high throughput sequencing, and a large bioinformatics support group as well. We have 10 BSL-3 suites, which are allowing much broader access by our research scientists to work on a wider variety of infectious agents than in our other facility, and many of them also include animal holding rooms to allow for animal BSL-3 work.

We have one suite that is dedicated to support sterile sorts and live cell confocal microscopy on BSL-3

agents, as well as BSL-2 and BSL-3 insectariums in the use facilities. We have dedicated suites designed to support microarray, PCR, NMR, mass spectrometry.

This is just a few screenshots of -- not screenshots. They are actual photographs, excuse me, of some of the equipment. We now have Illumina HiSeq, as well as several MiSeq sequencers to support next gen sequencing. This is the flow cytometry core, which includes special containment for BSL-2 and 3 live cell sorting.

High resolution mass spec, a very large suite to support NMR. We now have an 850-megahertz magnet to help us to prepare for even higher resolution structural information for things like biosimilars, and high resolution confocal and microscopy.

So finally, I'll just start where I finish, which is to thank again the site visit team, as well as you today, for your evaluation and thoughtful input into our program. Again, your review is really important for us to make sure we have high quality research to help fulfil our regulatory mission. So I'll stop there and answer any questions.

DR. DAUM: Thank you, Dr. Wilson, very much. The floor is open for committee clarifying questions for Dr. Wilson's presentation.

Hearing none, before I call on the next speaker, I would just like to commend CBER and the FDA in general, but particularly CBER, for conducting research like this and also for making it available for external and internal review on a regular basis. I think it's to be admired, and I think the proof is in the pudding. It's a wonderful program, and these reviews have been important eye openers I think for all of the committee. Thank you very much, Dr. Wilson.

Our next speaker is Dr. Chumakov, Konstantin Chumakov, who is the associate director for research at OVRR CBER, and Dr. Chumakov, the floor is yours.

Agenda Item: Overview of OVRR, Konstantin Chumakov, Ph.D., Associate Director for Research, OVRR, CBER, FDA

DR. CHUMAKOV: Thank you very much.

So I will give you a brief overview of the Office of Vaccines Research and Review and its activities. So our mission is to protect and enhance public health by assuring availability of safe and effective vaccines, allergenic extracts, and other related products.

So the office includes three divisions. Two of the divisions that are highlighted in green are what we call product divisions, and this is where researcher

regulators work, the concept that Dr. Wilson told you about. So they are doing whatever their names indicate, and there is also another division in the offices, the Division of Vaccines and Related Products Applications. This is the home of our fulltime reviewers, meaning that this division only does review, and all performs all regulatory actions.

So our portfolio includes a few dozen bacterial and viral vaccines that are either live or inactivated, and then a tremendous number of allergenic extracts. There are exceeding 2,000 individual products, and we also have another class of products under our purview, which are probiotics and other live biotherapeutics, and there is no licensed product in this category yet.

So our core activities are to review, evaluate, and take actions on all kinds of regulatory actions, biologics license applications, amendments and supplements, conducting inspections, and so on.

Another part of what we do is develop policies and guidances for industry and that govern premarket review of regulated products, and finally we also conduct intramural research related to the development, manufacture, and evaluation of vaccines and related products, and this is what I will be focusing in my

presentation.

So our key challenges are that in vaccines the biggest emphasis is on safety. For obvious reasons, they are used mostly for healthy individuals and for mass use of universal immunizations of children. So we also are very often facing very short regulatory cycle. For instance, a good example is influenza, when we need to complete our review within one year and also facing some emerging threats such as pandemic influenza for instance.

Also, many of our products are quite old. Some of them are a few centuries old. So that's why there is a need for innovative technologies to be introduced for manufacture and application of these old products. And that's why research plays a critical role in our regulation to address all these three challenges.

The purpose of our research program is based on the need to contribute to regulation of vaccines by addressing key scientific aspects that are critical for effective regulation of the products. We also work on development of methods for evaluation of these products in establishing standards and making sure that the evaluation of products is done based on the best science available.

We also look at our research program as a way to recruit and maintain highly trained scientists who have

expertise in a broad range of subjects that is key to our ability to respond to crisis, to new emerging threats, by having all the expertise needed for this in house.

Finally, I think we also provide some leadership to the vaccine industry by showing the way to introduce novel vaccine technologies and in general having highly respected scientists in our office gives us additional authority when we issue guidances and deal with industry as a kind of leading scientists in areas.

So our research priorities are trifold, and they are based on assuring safety, efficacy, and availability of products. So this is very clear that safety and efficacy are two cornerstones of any regulation. Availability is also important, because we also want to make sure that the manufacturing processes and nothing goes wrong so that vaccines that are developed and licensed are also available so that they can serve their purpose.

So what is the biggest challenge in this research management aspect? We are firm believers that good research can only be done based on investigator-initiated model, which has proven to be kind of working everywhere in academia and every other research institution, but we also have to reconcile it with our strictly defined agency mission. So that is why the challenge between the

grassroots initiative of investigators who propose their scope of their studies and the need to address critical aspects is a kind of balancing act that we need to address.

So what are the sources of scientific information that we use for making these decisions? Just like I have mentioned, our researcher regulator model ensures that scientists who participate in review are also doing research. So in fact that they are familiar with the current challenges facing the vaccine industry and regulatory process by being personally involved in regulation.

They also communicate with their peers in academia, science, and industry and other government agencies, and they do it by participating in scientific conferences, by publishing their own papers, and being immersed in the new developments that take place outside of the agency. Also, we are actively involved in international harmonizations. So a lot of our scientists serve on the various WHO panels and so on, and also deal with their peers in other countries.

Definitely we take advantage of advisory committee process, and this today we are kind of -- it's a part of this process. So we take advice from VRBPAC very seriously, and this is a site visit that every lab has to

go through every four years.

So since OVRR has a very wide range of projects, about 10 years ago we decided to set up a special research management committee that is called for a coordination of research process and the committee includes division directors and deputies, two representatives from the staff from each research division, as well as representatives and leadership from the review division to review the scope of our research program to make sure that there is no unnecessary duplication and that we cover all bases.

So that's what we do on our regular meetings. We identify gaps and redundancies, and also we make sure that the process by which resources are allocated is uniform across the office.

So each year, each principal investigator writes an annual report where the progress is documented as well as proposes the scope of research studies for the next fiscal year, and this research report is reviewed then by a lab chief, then by division directors. The broad scope of the overall research program is then reviewed by research management committee, and the ultimate decisions on resource allocation are made by division directors in collaboration with the immediate office of director of the office.

So what are the principles? So once we evaluate research programs and projects that are proposed by principal investigators, we take into account three major aspects. First of all is its public health significance, and here are some elements that go into this decision: public health need, meaning that there is a -- for instance, immediate regulatory relevance, some pending regulatory action that needs some input from research folks, or there is a strategic regulatory relevance. For instance, if we know that some class of products is coming on line, we need to make sure that we understand how to regulate it.

There is also a component that is based on scientific merit. We definitely want to fund only the best scientifically meritorious projects, and we take into account scientific rationale, originality, feasibility, and so on, and of course, finally we also have to take into account the qualifications of the investigator who proposes research and past productivity and impact.

So just before I finish, I wanted to give you a flavor of how our funding is structured. So this is the numbers for last fiscal year, and as you can see, roughly half of all funding in the office, funding that went into research, was what we call operating dollars, meaning that

this is what office received to support research programs.

Then, three other sectors marked pandemic flu, modernizing science, and critical path are also agency money, but that was distributed based on the peer review process that took place at the central level, and also there are several other streams of funding, such as MCM, Office of Minority Health, and PDUFA. This is something that also came from the agency funding.

So as you see, it's about 80, 85 percent of our funding comes from the money appropriated by the Congress, and the rest is what our investigators bring in the form of grants. For instance, some support that we get from BARDA, interagency agreements with NIH, CDC, some CRADAs with other entities, as well as royalties. So this is a kind of structure. So this is the source of our support for research program.

And I think this is my last slide, and I thank you for your attention.

DR. DAUM: Thank you very much, Dr. Chumakov. Are there clarifying questions on Dr. Chumakov's presentation from committee members?

DR. SAWYER: Hi, this is Mark Sawyer. I don't have a question, but I need to report I have lost the webcast and have been following along on the PowerPoint

slides that were sent out, which work for me if I'm the only one who lost the connection.

DR. LONG: I have lost it, too.

DR. VIJH: Could you try it again, because Dr. Moore reported it, and then now he is able to watch it?

DR. ENGLUND: I was able to log in again.

DR. VIJH: We have been having trouble.

DR. DAUM: Dr. Vijh, is it okay if members that lose it like this email you?

DR. VIJH: Yes, if they can follow the presentation, the slides, and they can email me, but the IT staff is aware of the issue. So I have been conveying it to them.

DR. MOORE: Just one quick follow-up on that. Sujata sent me an email that has the link in it again.

DR. DAUM: Thank you very much, Dr. Moore. Are there any clarifying questions from committee members? If not, I thank Dr. Chumakov very much for your presentation, and we will next go to Dr. Weir, who is the director of the Division of Viral Products of CBER, to give us his overview of DVP.

Dr. Weir?

Agenda Item: Overview of DVP, Jerry Weir, Ph.D., Director, DVP, CBER, FDA

DR. WEIR: Thank you and good afternoon. I am going to give a quick overview of the Division of Viral Products. It should be pretty brief.

The division is divided into seven laboratories, the names of which roughly but not perfectly mirror the regulatory responsibilities of the individual lab. The one under review today, the Laboratory of Method Development, actually probably does not reflect their regulatory responsibilities very well, but I think that Dr. Rubin will go into that in just a moment.

The mission and the functions of the laboratories for the Division of Viral Products can be summarized in two bullets. One, we regulate viral vaccines and related biological products, ensuring their safety and efficacy for human use. We also try to facilitate the development, evaluation, and licensure of new viral vaccines that positively impact the public health. We have quite a few responsibilities to meet to try to meet those goals. They are listed on the next slide.

They include investigational new drug and biologics license application review, as well as other premarketing activities: for example, pre-INDs and IND meetings. The staff is involved in BLA supplement review, lot release review, and other post-marketing activities,

also biological product deviations. Any time something goes wrong with a product that is already manufactured and licensed, the staff participate in manufacturing inspections. This is both pre- and post-licensure, and we have a fairly heavy consultative role with other public health agencies, including the World Health Organization, our colleagues at CDC, and other agencies such as NIBSC in the UK, and last but not least, the staff conduct research that is related to the development, manufacture, and evaluation and testing of viral vaccines.

The role of research in the Division of Viral Products is summarized in the next slide. The research and the laboratory activities are designed to complement the regulatory mission. We address issues related to regulated viral vaccines. We also try to anticipate and address issues related to the development and evaluation of new viral vaccine products. Sometimes these are very general issues applicable to many products or product classes. Sometimes on occasion they are very specific product issues which must be addressed to help us with our review and evaluation.

The next slide gives a quick snapshot of the budget and the staff in the Division of Viral Products for the last fiscal year. There were about 77 fulltime

equivalents. These are government employees. This staff is supplemented by anywhere between 40 and 50 contract employees. Most of these are postdoctoral fellows, but also some postbac students, and these are usually but not always, but almost always, supported through our external program called the ORISE program. Most of these staff are supported by targeted funds and external grants and contracts. A few are supported directly out of our base operating budget.

Last year, the division budget FY15 had a standard operating budget of a little over $4 million. There was a lot of targeted support, nearly $2 million. These included the categories that Dr. Chumakov just mentioned: pandemic influenza, modernizing science, critical path. It was also supplemented by nearly another million dollars in medical countermeasures. A lot of this was Ebola funding last year. Then we had external DVP funds that totaled about $1.6 million.

All totaled, that added up to for us a very good year, and I think most laboratories were well supported last year for their research activities.

At this point in time in January, we do not have a budget for the coming year, and so we will just keep our fingers crossed that hopefully we will have another good

year.

The staff of the division, the FTEs, I have listed on the next slide divided up by laboratory. You see there is some variability. There is also a different number. There are different numbers of principal investigators in each of these labs. Again, this reflects somewhat a lot of factors but include the different responsibilities held by each laboratory. The Laboratory of Method Development is actually one of the larger of the labs.

Finally, the site visit evaluation that we are here today to discuss, this includes the program review and assessment of the progress on the different projects that were presented and pursued since the previous site visit. It includes individual review, particularly if certain individuals are up for promotion and tenure, and as always, we evaluate -- we appreciate your evaluation of future directions and any input you would like to give us.

I'll stop there.

DR. DAUM: Dr. Weir, thank you very much. Are there any clarifying questions from the committee on Dr. Weir's presentation?

Hearing none, we will move right on to Dr. Steven Rubin's presentation.

Dr. Rubin -- I presume you are here, because you are walking to the podium -- is the acting laboratory chief of the Laboratory of Methods Development of the Division of Viral Products and who will give us an overview of the laboratory. Dr. Rubin?

Agenda Item: Overview of LMD, Steven Rubin, Ph.D., Acting Laboratory Chief, LMD, DVP, CBER, FDA

DR. RUBIN: Thank you. I will just give a quick overview of the lab. Our mission is to conduct research that leads to the creation of new concepts, methods, and reagents for quality control and evaluation, not only of new vaccines and vaccines that are in development, but also of existing vaccines that we have had in our portfolio for many years.

The history of LMD is briefly summarized in this slide. The top level row shows that the Laboratory of Methods Development originated in a different division, the Division of Product Quality and Control that's shown in green. In the late 1990s, this lab was moved over into the Division of Viral Products, and during most of that time, as shown in the yellow bar, Dr. Konstantin Chumakov was the chief of that lab until very recently where I took over in that role about a year ago.

The various site visits are shown here as well,

and also dates when key members have joined the lab are indicated here, color-coded by group as to where they belong. Not so important for this discussion, but maybe for the review of the materials that you have.

The research programs are divided by PI. We have three PIs. Each PI has their own research program. Dr. Chumakov's program is mostly centered around the genetic and antigenic consistency of vaccines. These are the individuals in Dr. Chumakov's group. You have the slide, so I don't need to belabor the point and go over each individual.

I will just give a brief overview of some examples of types of work that is done in this group. One is development of tools for monitoring the genetic stability of viral vaccines. Shown in the graph here is one example. This shows the genetic haplotype, so to speak, of the quasi-species of oral poliovirus vaccine type 3, and what Dr. Chumakov has shown many years ago is that the particular mutation at position 472, shown here in the red bar, this is in the internal ribosome enterocyte within the virus; when that mutation exists at one percent or less, the nonhuman primate model that is used for lot release, those animals do not develop neuropathology. Animals, vaccine lots that are higher than this, if tested

typically are hot and it fails neurovirulent safety testing.

So this is one method of kind of refining testing to get away from more generic, less informative animal-based tests to more specific molecular biology tests, and something like this is currently being evaluated and discussed at the WHO.

Other projects focus around the design of genetically stable attenuated poliovirus vaccines. This is done either by changing CpG content or using codon pair bias, as well as a number of other approaches.

Finally, a metagenomic based method of doing surveillance for environmental samples, such as looking at pathogenic viruses. This graph here shows the results of that from deep sequence data. This is a single sewage sample that was crudely purified and nucleic acids were extracted and were amplified in sequence, and here the database was just queried for alignments of all the enteroviruses within that sample. So this shows things like Coxsackieviruses, polio, ECHO viruses, and all the other enterovirus, 68, 71, et cetera. So this is a method of very rapidly separating out and identifying each individual virus that is within a sample.

Dr. Chizhikov is a second PI in our group. His

research program is mostly focused on detection of adventitious agents as it pertains to vaccine manufacturing. These are the individuals in his group, and some examples of his project recently, which was discussed at the site visit, was the tangential flow filtration method of purifying samples followed by deep sequencing for detection of adventitious agents.

He has also been involved for many years in developing alternatives to the current mycoplasma testing requirement that we have in our CFR. We had hoped that we could eventually get away from the more time-consuming, laborious, and expensive culture-based methods and use nucleic acid based testing, and he has developed a number of reference strains through international collaborations, and hopefully that effort will be successful soon.

One final example is development of in vitro alternatives to the current lethality-based method of testing of testing rabies virus potency. This has been an effort that a lot of people have championed for years, and he has made a lot of good progress in that as well.

These are just a few examples at each of these labs. Certainly it is not all of the work that is being done.

My group's focus is mostly on identifying the

molecular basis of viral virulence and attenuation. These are the individuals in my group. Unfortunately, the last two individuals are leaving at the end of this month.

One of the projects is to identify genetic markers of virus attenuation. The way we do this is we obtain, say, a virulent clinical isolate. We are able to attenuate it in the lab, and then we take genes from the attenuated variant and replace those with genes of the virulent virus and vice versa to make these recombinant chimeric viruses, rescue them in cell culture system, and test them in animal models to identify the role of specific genes in virulence or attenuation or specific regions within genes or even specific nucleotide changes.

We also recently started another project on working to identify cellular targets of the virus in the host; in this case, this example, is a cell culture system that is infected on the left side with -- I think this is RSV and that it expresses enhanced green fluorescent protein versus using the same virus in these cells that were treated with siRNA against NF-kappa B2, and you can see that that completely abrogates expression of virus almost. So this kind of information not only could be used to help with the design of future vaccines, but also could help in the creation of cell substrates that could be used

in the manufacture that perhaps could be more permissive to virus infection getting larger yields.

Finally, one long-term project that we have had for many, many years is the investigation of mumps outbreaks. These continue to occur in the United States, despite the fact that we have excellent vaccine coverage in this country. Remarkably, just about all of these cases occur in people who have been vaccinated, not because the vaccine is causing mumps, just because just about everybody is vaccinated.

What we have shown in collaboration with the CDC is that there is significant decline of antibody titers against mumps virus with time post-vaccination, and that is also supported by this graph shown here, which is a review of the literature that we did showing that the vaccine effectiveness wanes over time as a function of when the individual was vaccinated. So we are working on projects right now to improve existing vaccines, specifically to improve the B cell memory and antibody avidity.

This shows the total publications that we had during the site visit review period, which was July 2011 to July 2015, a total of 52 publications in some very good journals. You have all that information, I believe, in the packet from the site visit committee.

As Dr. Wilson had mentioned earlier, we don't just do -- our researchers are not strictly doing research. They have a large regulatory portfolio they are responsible for. Our laboratory in particular has a very high regulatory review burden. We review all of these submissions from industry dealing with poliovirus vaccines, the multiple families of measles, mumps, rubella and varicella vaccines in combinations, rotavirus, rabies, some influenza virus, not as much as before. We have a different group within DVP that primarily reviews these, but nonetheless, occasionally we do help out with those reviews.

And we have an equal amount of investigational vaccines that we review. The Ebola vaccine is one I'm sure everyone has heard about that seems to be doing quite well. We have a number of others that for proprietary reasons I can't go into them; hopefully we will be hearing about these soon, not in terms of the disease they cause but rather the vaccines that are being developed to prevent them.

We do a lot of lot release activity. Every lot of vaccine that the manufacturer wants to release, that comes to the FDA first. The release data for that is reviewed by our staff and signed off before it's released

to market. We regularly participate in domestic and international vaccine manufacturing facility inspections, and quite active in drafting guidance documents for industry.

This is an overview of the regulatory activity during the site visit review period between 2011 and 2015, broken down by master files, investigational new drug applications, and biologic license applications, and you can see there's a total of 601 during that time, which is quite a large number. I only bring this up to just kind of reinforce the idea that it's not 100 percent research. So a lot of our research accomplishments are accomplished in the face of a lot of other responsibilities.

This is a list of some guidance documents that we have drafted between -- I said since last site visit. This was a slide from the site visit. So again between 2011 and 2015. These are guidances on process validation and other CMC-related guidances as well as animal rule guidances, activities for genetically engineered animals and expression products, and most recently guidance on clinical development of Ebola vaccines.

I think this is my final slide. This shows a list of the international activities that we are involved in, which is kind of a nice blend of some of our regulatory

and review work: advising WHO on vaccine issues, a number of international workshops that we actually have taken a lead role on from poliovirus vaccines, rabies vaccines, Ebola virus and mycoplasma test methods, as well as a number of other international activities. Examples are the Global Virus Network, Task Force for Global Health, and the Bill and Melinda Gates Foundation consortium on poliovirus vaccines. Most of these deal with poliovirus, but there are a number of others as well.

I believe this is my last slide.

Agenda Item: Questions

DR. DAUM: Dr. Rubin, what a tour de force. Thank you very much for presenting that. We have an opportunity for committee members to ask you clarifying questions about your presentation.

Hearing none, I would like to open the floor to general committee input into any of the presentations that you have just heard.

I am going to turn the floor over to Sujata to please read the open public hearing statement. Can we have it early, Sujata?

Agenda Item: Open Public Hearing

DR. VIJH: Yes, I think we don't see any public members that wanted to make a comment. So I don't have to

read the statement. There is nobody around here.

We would like to take a minute to get the webcast stopped and just rearrange and Dr. Filip Dubovsky is going to leave the teleconference.

And give us a minute, and the members, could you please just stay on the phone, and I'll just go check that the webcast is being stopped.

Thank you.

(Whereupon, the open session was adjourned at 1:55 p.m.)