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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE
MEETING ON CBER LABORATORY SITE VISITS
LABORATORY OF MYCOBACTERIAL DISEASES AND CELLULAR
IMMUNOLOGY
LABORATORY OF METHOD DEVELOPMENT
OPEN MEETING BY TELECONFERENCE

Thursday, May 8, 2003

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Jerry Weir, Ph.D.

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William Egan, Ph.D.

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P R O C E E D I N G S

Call to Order and Announcements

DR. SACHS: We are still waiting for about three more people to connect but, in the meantime, our Chair is on, Dr. David Stephens, I would just like to start with a roll call because that may take five minutes, just to go through people's names.

When I call your name just take your "mute" button off and say "present" and then you can put your "mute" button back on, please.

I would just like to briefly do the introductions. Dr. David Stephens, Professor of Medicine, Division of Infectious Diseases Department of Medicine at Emory University School of Medicine.

DR. STEPHENS: Here.

DR. SACHS: Dr. Ruth Karron, Associate Professor, Division of Disease Control Department of International Health at Johns Hopkins University, School of Hygiene and Public Health.

DR. KARRON: Here.

DR. SACHS: Dr. Michael Decker, Vice President, Scientific and Medical Affairs, Adventis Pasteur.

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DR. DECKER: Here.

DR. SACHS: Dr. Pam Diaz will be joining us a little bit later but I will go ahead with the introduction. She is Director of Infectious Diseases at Chicago Department of Health.

Dr. Judith Goldberg, Director, New York University School of Medicine, Division of Biostatistics. We are still waiting for her to connect.

Dr. Sam Katz, Department of Pediatrics, Chairman Emeritus at Duke University will not be able to attend this call.

Dr. David Markovitz, Professor, Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Medical Center.

DR. MARKOVITZ: Thank you.

DR. SACHS: Thank you. Dr. Audrey Manley, President Emeritus, Spelman College, Rear Admiral U.S. Public Health Service.

DR. MANLEY: Here.

DR. SACHS: Dr. Gary Overturf, Professor of Pediatrics, Department of Pediatrics, University of New Mexico School of Medicine.

DR. OVERTURF: Here.

DR. SACHS: Thank you. Dr. Peter Palese,

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Chairman and Professor, Department of Microbiology,
Mt. Sinai School of Medicine of New York
University.

DR. PALESE: Yes, I am here.

DR. SACHS: Thank you. Dr. Julie
Parsonnet, Associate Professor of Medicine and of
Health Research and Policy, Stanford University.

DR. PARSONNET: I am here.

DR. SACHS: Thank you. Dr. Walter Royal,
Associate Professor of Medicine, Morehouse School
of Medicine.

DR. ROYAL: Here I am.

DR. SACHS: Thank you. Dr. Richard
Whitley, Professor of Pediatrics, Microbiology and
Medicine, Department of Pediatrics and
Microbiology, University of Alabama at Birmingham.

DR. WHITLEY: I am here.

DR. SACHS: Thank you. Dr. Diane Griffin,
Professor and Chair, Molecular Microbiology and
Immunology, Johns Hopkins University School of
Medicine.

DR. GRIFFIN: Here.

DR. SACHS: Thank you. Ms. Barbara Loe
Fisher, Co-Founder and President, National Vaccine
Information Center.

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MS. FISHER: I am here.

DR. SACHS: Right now, just to repeat, Dr. Pam Diaz will be joining us a little later and when Dr. Judith Goldberg gets on, hopefully, she will introduce herself and let us know.

DR. GOLDBERG: I am on.

DR. SACHS: Oh, great. Thank you very much. I just want to welcome everybody. I am Dr. Jody Sachs, the Executive Secretary for today's meeting of the Vaccine and Related Biological Products Advisory Committee. I would like to welcome you to the 96th meeting of the advisory committee.

There is a speaker phone, and public participation is welcome, located at the FDA Building 29B at the NIH campus in Conference Room A, in Bethesda, Maryland.

This afternoon will consist of presentations and committee discussion that are open to the public, as described in the Federal Register notice of April 14, 2003. Should a committee member get dropped from the teleconference, simply call back at the 1-8800 line and ask to be connected, giving the pass code number 15856 and the operator will connect you

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again. If you have any problems while on the call, press zero and the operator will help you. We ask that you do not place us on hold because many clinical centers have background music and it can

be very distracting to those on the conference line. However, I strongly urge everyone to use the "star-6" as a mute except for Dr. Walter Royal. He is right now in Italy and I don't want him to be disconnected. There are many lines and the "mute" button will help with the background sound. Remember if you are going to speak to take your "mute" button off before speaking.

I also just want to tell you who is in the room right now. The FDA staff members who are participating in today's meeting are currently seated in the room. Right now Dr. Karen Midthun, Director of the Office of Vaccines Research and Review; Dr. William Egan, Deputy Director, Office of Vaccines Research and Review; Dr. Jerry Weir, Division Director of Viral Products; Dr. Richard Walker, Division Director of Bacterial, Parasitic and Allergenic Products; Dr. Kathryn Carbone, Acting Associate Director of Research.

We have a court reporter here who will take minutes for the meeting so I want to urge

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everybody to identify themselves each and every time they talk. The transcriber cannot see who you are and I, please, ask your assistance and help in order to attribute the comments to the appropriate committee member. I also want to remind you not to be using a cell phone at the moment. It presents unnecessary background noise to the line.

At this time I would like to read a conflict of interest statement for the record. I am sorry, I was just reminded that there are speakers today who need to be introduced whom I didn't mention but who are in the room with me right now. Chief of the Laboratory of Mycobacterial Diseases and Cellular Immunology, Dr. Sheldon Morris and Chief of the Laboratory of Method Development, Dr. Konstantin Chumakov. They are both seated in the room with me at the moment so I wanted to let you know, and they will be speaking today in the open session.

I would like to address the conflict of interest statement for the record. The following announcement addresses conflict of interest issues associated with this meeting of the Vaccines and Related Biological Products Advisory Committee on May 8th, 2003.

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Based on the agenda made available, it has been determined that the committee discussions present no potential for a conflict of interest.

The Director of the Center for Biologics Evaluation and Research has appointed Ms. Barbara Fisher and Dr. Diane Griffin as temporary voting members for the committee discussions.

In the event that the discussions involve specific products or firms not on the agenda for which the members and consultants have a financial

interest, the members and consultants are aware of the need to exclude themselves from the discussion. Their exclusion will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that you address any current or previous financial involvement with any firm whose product you wish to comment upon.

I also want to mention that Denise Royster is here in the room with me. Denise is the committee management specialist that is responsible for pulling this meeting together and I am very indebted to her.

This ends the reading of the conflict of

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interest statement and, Dr. Stephens, before we begin the agenda I just wanted to address a result from a survey that was completed by GSA and Gallup people on advisory committee overall performance.

I tried to give everybody the results of the survey by e-mail and I just want to briefly comment and touch upon it so that it can be opened at a later time if you had any comments or concerns that you wanted to bring up we could discuss it as you wish. But, briefly, if you turn to that survey, if it is in front of you, there was a whole day meeting to actually discuss the interpretation of the results.

I didn't want to go into it in depth but I did want to tell you briefly what it meant and how to use this in terms of what benefit we can even gain by looking at an overall survey of advisory committees.

Basically, there were seven responses from the Vaccine Advisory Committee members. So, that means that half the members responded in the survey and half the members didn't. But what it can tell you when you look at the results is that we do fall above average within the government-wide results, and within the agency results we are a little bit

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higher in our overall mean score.

When you look at the analysis, they look at the top five percent and they call it a top box. They are looking at how many people actually scored the highest. That is actually the best performance. If you look at the best things that were commented on and what we do best in Vaccines Advisory Committee, there are actually a few statements that I can read: Our committee meetings run well. Our staff is well prepared. Access to senior management and technical experts is good. The agency is more effective because of our advisory committee. We help build trust in the government and the committee results are available to others. These are the ones that we scored the top, the best in terms of the overall highest

ranking.

The ones in the areas that we really need to look at in terms of what improvement can be found by the results, I am just going to mention a couple and those are the ones that we scored pretty much the lowest, meaning that there were the least amount of number five's, meaning the highest score. They were, our committee is made up of the right mix of individuals. The next one is our committee

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receives sufficient feedback from agency on recommendations or on other contributions.

That doesn't mean that we are not doing well in those areas. Those are the areas that are up for improvement. If anybody feels that they want to comment on that, now is fine; later by e-mail is fine. If there are things you can think of that would make the committee better in how it is run by the right mix of people or by feedback from the meetings back to you so you know the results, please feel free to comment at any time. I can welcome the comments now and open them up for a later time also.

I just wanted to give you some results quickly. On the last page, before I open it up to everybody, there is an overall page that has the importance-performance leverage analysis. It has a bunch of numbers in a square or a box. This is the overall government-wide performance. If you look

at the top right box, that is the best. If you look at the lower left box, that is the worst.

So, the questions are numbered and the best are in the right-hand corner of the upper box. That is an easy glance, you know, overall how the government performs on advisory committees.

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Overall we did very well and I just wanted to give you that quick feedback. I am really pleased that we are a well-run advisory committee but there are always areas we can look at for improvement and I also wanted to leave that open at this point and any other points. So, I will leave it open right now. If there is anyone that would like to comment, please feel free.

DR. STEPHENS: Jody, this is David Stephens. Can you give us a little more background about this survey, like the time frame and the N of seven, is that members of the committee who were asked to complete this, all members of the committee?

DR. SACHS: I believe that a certain amount of surveys were sent to the committee members. I know that there were seven responses. It was back in November of 2002. I know, for example, there was someone who attended the meeting I went to who actually filled out the survey. That was Dixie Snyder. But I can't tell you who else filled out the survey because I don't have that

information.

DR. STEPHENS: It was striking to me that the number of participants who filled out the

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survey said that the right mix of individuals was zero.

DR. SACHS: That is misleading. That means that there were no number five's. Five is the highest score you can get.

DR. STEPHENS: I see.

DR. SACHS: So, it doesn't mean that the right mix is zero; it means that nobody responded to the highest score. When you think about the highest score you think about, well, you would be willing to testify in Congress. If you had to, you would swear to it. That means that you are pretty sure of it. Well, nobody was pretty sure of it. That is all it means. It doesn't mean that we scored zero.

DR. STEPHENS: I see. What about this received feedback from agency, sufficient feedback from agency?

DR. SACHS: Again, those are the two areas we can improve and I am not really certain, without talking to the individuals who filled out the survey, what they would like to hear back. I know I have been trying to send back results on new products that are approved. As soon as they are approved I do try to forward that information to

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all committee members and let them know what web site it is on so they can get more information. But maybe what they are talking about is right after the meeting is over they don't get sufficient information to know what results are acted upon. I am not really certain; I can only guess but if anyone has any comments, please feel free.

DR. STEPHENS: Any comments or questions for Jody about this? Insights?

[No response.]

DR. SACHS: At this point, if no one wishes to make a comment, think about it and you can comment to me by e-mail to me later. Again, I will be happy to open it up for discussion at a later time. But at this point I do want to go ahead with the agenda and turn the meeting over to our Chair to start the agenda and our meeting so it can officially begin. At this point, our first speaker is Dr. Richard Walker and I will turn the meeting over to Dr. Stephens. Thank you.

DR. STEPHENS: Thank you very much, Jody. Let's go right ahead. Dr. Walker will give us an overview of the Division of Bacterial, Parasitic and Allergenic Products.

Overview of Division of Bacterial, Parasitic and

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Allergenic Products

DR. WALKER: Thank you and good afternoon. In the next few minutes I will give you an overview of the Division of Bacterial, Parasitic and Allergenic Products with the hope that it will give you an orientation that will be useful in your subsequent evaluation of the Laboratory of Mycobacterial Diseases and Cellular Immunology.

Some of the points that I would like to hit would be the mission and functions of the division. Basically, those are to assure safe and effective products for immunological control of bacterial, parasitic and allergenic agents affecting human health. Most of the people involved in that endeavor are what we call researcher reviewers. They conduct research of their own and you will be hearing some of that from Dr. Morris in a few minutes. They also review products coming in.

In addition to that, our people are involved in a number of other activities like inspections of various vaccine production facilities, lot release testing or protocol review for lot release testing, label/promotional activity review. In addition to that, since we have product

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experts in a number of disease areas, these people provide consultations for outside organizations, like PAHO and WHO.

The next point that I would like to make

is that we really have a cradle to grave relationship with a product and the next two slides, as pointed out here, are that the role in our regulatory review approval starts with pre-IND where we start meeting with the sponsors and begin providing guidance. Then, although not so important, are the various tasks we are involved in the various stages of a product's life, but just to emphasize that we are not only dealing with a product when the IND comes in and the activities towards licensure of that product, but even post-licensure we are still involved with the product. So it is, like I said, a cradle to grave relationship.

The other point I would like to make is, as you might guess from the name of our division, that we have a wide variety of products that we need to be prepared to address. There are two slides labeled "new or improved products possible in the next ten years." That just gives an example, whether you are talking about respiratory

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pathogens or special pathogens such as Bacillus anthracis, Yersinia pestis and other bioterrorism agents, sexually transmitted pathogens, diarrhea-causing pathogens and so forth, as well as allergenic products, the cockroach antigens and skin test antigens. So, we have quite a variety of things that we are trying to deal with in this

division.

To accomplish that, the division, as shown on the next slide, is organized into eight laboratories so there is the Immediate Office of the Director where I am. Also, we have a regulatory staff and an administrative staff. Then we have two laboratories that provide sort of research expertise that cuts across areas. One is the Laboratory of Biophysics under Dr. Pastor. The other is the Laboratory of Methods Development and Quality Control under Dr. Meade. Then there are the six product laboratories. There is the Laboratory of Respiratory and Special Pathogens under Dr. Burns; the Laboratory of Bacterial Toxins under Dr. Vann; the Laboratory of Mycobacterial Diseases and Cellular Immunology, that we will be discussing today, under Dr. Morris; the Laboratory of Bacterial Polysaccharides under Dr. Frasch; the

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Laboratory of Enteric and Sexually Transmitted Diseases under Dr. Kopecko; and the Laboratory of Immunobiochemistry, which are the allergenic type products, under Dr. Slater.

I don't want to spend a lot of time on the next slide but it just shows some of the major thrust areas within the division, and it shows how in some cases a number of the laboratories is indicated by those various abbreviations under the bullet that are involved in those activities. I

really don't want to spend a lot of time on that slide.

The one thing though that I would like to hit that has been a major impact not only in Dr. Morris' laboratory but in a lot of the laboratories in the division these past two years has been the growth of the bioterrorism program. We now have research/review going for the major bacterial bioterrorism agents, *Bacillus anthracis*, *Francisella tularensis*, *Yersinia pestis* and Botulinum toxin.

I am not going to spend a lot of time talking about the different laboratories. The Laboratory of Methods Development and Quality Control really provides standardization of testing

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and is involved also in our lab accreditation activities.

The Laboratory of Bacterial Polysaccharides is concerned with immunochemical and physical chemical characterization of various polysaccharide and conjugate vaccines.

The Laboratory of Biophysics has some of the very sophisticated technologies that are needed by laboratories, like the Laboratory of Bacterial Polysaccharides that I just mentioned, to characterize those vaccines or vaccine components using such things as light scattering and NMR.

The Laboratory of Respiratory and Special

Pathogens used to be predominantly focused on pertussis work but in recent years has expanded its activities to Bacillus anthracis and Yersinia studies.

The Laboratory of Bacterial Toxins is dealing now with neurotoxins, corynebacterium regulation of virulence vector production by that organism and glycobiology. I am not going to say any more about the Laboratory of Mycobacterial Diseases and Cellular Immunology because Dr. Morris will cover that in a few minutes.

The Laboratory of Enteric and Sexually

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Transmitted Diseases are doing studies involving invasive mechanisms of certain enteric pathogens like Shigella and Campylobacter. They are studying genetic regulation of bacterial virulence genes and, because this may be important to vaccines in the future, there is new activity in that group studying mucosal immunization techniques and trying to understand mucosal immune responses to vaccine products.

The last laboratory, the Laboratory of Immunobiochemistry deals with the immunological reactions to allergenic products and trying to understand those, as well as characterization, structure and function of allergens.

An important point, and maybe Dr. Weir will emphasize this when he gets to his group, but

something that you need to keep in mind when evaluating our research reviewers is sort of the environment they work in and some of the hurdles they have to deal with. Of course, some of those hurdles are the same as you have in any organization. If you have a large organization you have a bureaucracy, whether it is personnel, supply or anything else, and sometimes those can be a challenge. But that is not unique to FDA. It is

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something that is characteristic of government organizations and includes us. Funding levels can be uncertain from year to year and are dependent upon the appropriation process.

But the most unique challenge I think faced by our researcher reviewers is that the timing of the workload that is determined by the sponsor submissions and not by us. So, we don't know when a new IND or any other thing is coming in and then, once it comes in, we have to deal with that in a certain time frame. So, a good part of our workload is determined by people outside of our organization.

Finally, the thing that I ask the committee to do, and hope will be discussed a little bit more later, is to review the individuals within the Laboratory of Mycobacterial Diseases and Cellular Immunology, evaluate their program and then also give us comments on what you think our

future direction should be. So, that is a brief overview of our division and if there are any questions at this time, I will be happy to answer them or we can come back to those later, whichever you want to do.

DR. STEPHENS: Thank you very much, Dr.

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Walker. I think we will take questions at this point. I don't hear any. I think in the interest of time, why don't we move to the overview of the Division of Viral Products with Dr. Weir?

Overview of Division of Viral Products

DR. WEIR: Thank you. My overview for the Division of Viral Products will be fairly brief and will be essentially the same outline as I gave the Site Visit Committee on January 9th, when they came to review the Laboratory of Methods Development.

The Division of Viral Products is one of three divisions within the Office of Vaccine Research and Review. We are one of the two product research divisions in this office. Besides myself in the Office of the Director, the Deputy Director is Philip Krause. We have seven laboratories roughly divided according to review responsibility in areas of research. They are the Laboratory of Hepatitis Viruses, the Laboratory of Vector-Borne Viral Diseases, the Laboratory of Retrovirus Research, the Laboratory of DNA Viruses, the Laboratory of Pediatric and Respiratory Diseases,

the Laboratory of Immunoregulation and, the subject of this particular site visit, the Laboratory of Methods Development.

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The mission and functions of the division can be simply stated as follows, we are responsible for and we regulate viral vaccines and related biological products. In addition, we are responsible for facilitating the development, evaluation and licensure of new viral vaccines that positively impact the public health.

The way that we meet these responsibilities and fulfill this mission is basically through our review activities and our research efforts. You have probably seen some of this in your background information and Dr. Walker has already mentioned a little bit of it as well, our review activities are multi-fold. They include the review of investigational new drug applications, or INDs; the review of biological license applications and their supplements. We also have lot release review and testing responsibilities; multiple post-marketing activities, and we participate in manufacture inspections.

Our research efforts are fairly broad and they are both applied and fundamental. They address different areas of viral pathogenesis; vaccine development and evaluation; viral vector

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evaluation. We have studies on vaccine safety and efficacy and we have various types of methods development.

The brief overview of the staff and the budget for the division is that at the current time we have staff of approximately 80 full-time employees, full-time FDA equivalent. The total staff of the division is about 120 because of the use of contract employees such as post-doctoral fellows. We have had a recent increase in the current fiscal year, FY02, of 13 full-time staff. This was a result of a counter-bioterrorism initiative.

The budget for the current year--as most of you know, the current year for the federal government is October 1 through September 30th--the current year budget is approximately a million dollars for the division. This was an increase from a low a few years ago of \$750K-80K approximately during FY99 and 2000 but it is actually a slight decrease from last year in spite of the added staff.

I think you have also seen in your briefing package that we have substantial supplemental funding at the present time from

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outside sources. It is now actually greater than

our internal funding. The Laboratory of Methods Development has been particularly successful at obtaining outside funding to support their research activities.

I am not going to go into detail about the research efforts in this laboratory. Dr. Chumakov will do this in just a minute. But I list two or three examples just to sort of give you an overview of what they do. Some of their efforts have been the development of molecular tests, such as MAPREC and microarrays. They have also been heavily involved in the development of animal models such as the transgenic mouse for neurovirulence assays for polio virus. And, they are also heavily involved in the development of various types of in vitro tests, such as IPV ELISA. The major regulatory responsibility of this laboratory is the regulation of polio virus vaccines.

This laboratory had its site visit evaluation on January 9th of this year, 2003. At that site visit the committee was asked to do three things: First, review the research programs within the laboratory; evaluate the progress of individuals in the laboratory and assess the future

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directions of the laboratory.

That is my brief summary. If anyone has any questions, I would be happy to try to answer them.

DR. STEPHENS: Thank you very much, Dr. Weir. Can you elaborate just briefly on the outside funding that appears to be increasing in the division, the sources of that funding?

DR. WEIR: Sure, you mean the types of funding?

DR. STEPHENS: Yes.

DR. WEIR: Yes, Dr. Chumakov can answer some of this too but essentially it is usually always fairly well integrated with the mission of the laboratory in the division. Dr. Chumakov's group, for example, has had various types of funding and DRPA is one example to support the same type of methods development that his laboratory is interested in and the division is interested in. So, there have been several sources. Another one is the National Vaccine Program Office.

DR. STEPHENS: Thank you. Other questions for Dr. Weir?

[No response.]

Thank you very much. Why don't we move

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now to the Laboratory of Mycobacterial Diseases and Cellular Immunology with Dr. Morris?

Overview of Laboratory of Mycobacterial Diseases
and Cellular Immunology

DR. MORRIS: Thank you. Can you hear me? I am going to provide just a brief overview of our lab in terms of the personnel and research

interests. I will briefly talk about our regulatory responsibilities and then talk about how we are involved with the public health community and the scientific community.

We basically have three sections in our lab, molecular vaccines, mycopathogenesis and immune mechanisms lab. I am the P.I. of the molecular vaccines section. I currently have two fellows and a technical person. I have included collaborators for each section just because the FDA is supposed to leverage resources here, but we have a number of collaborators including people at the Center for Devices and Radiological Health at the FDA, Vaccine Research Center at NIH, Child Health at NIH, Albert Einstein and the Southern Research Institute.

Our primary focus in the past five years in my section has been development of novel TB DNA

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vaccines and the characterization of attenuated Mtb strains. That is in collaboration with Bill Jacobs' lab at Albert Einstein. We have a mouse model for pulmonary TB that we utilize in our lab. In the past, in the mid '90s, we were concentrated on identifying drug resistance mechanisms. That effort continues at a low level today but most of our efforts recently have been on characterization of these novel vaccines.

The mycopathogenesis section is headed by

Mike Brennan. He has three Ph.D. level people working with him and a number of collaborators, including people from Institut Pasteur, Johns Hopkins, CDC, company Corixa, Albert Einstein and University of Sassari in Italy.

Mike's group is currently focusing on two projects, first of all, characterization of an adhesin of TB which they are looking at as a vaccine candidate, and also characterization of the novel PE gene family of TB. When the sequence became available of the TB genome in 1998, in the sequence it was realized there were a hundred or so genes that were related. The function of these genes is unknown and Mike's group has been at least partially characterizing some of these genes in

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this unique gene family.

Finally, the new mechanisms section of which Karen Elkins is the P.I. Because of the increased counter-bioterrorism funding in the past two years she has been able to build up her group. She currently has three fellows and three technicians. She has a number of collaborators, and I have only listed a few here, from all over the country.

Karen's main focus has been trying to identify mechanisms of protective immunity to intracellular pathogens; more specifically, to determine the basis of innate immune responses to

LVS, which is a live vaccine strain of *Franciscella tularensis* which happens to be a pathogen in mice and vaccine in humans. Secondly, to determine the role of B cells in immunity to LVS and Mtb and, finally, to elucidate the protective T cell-mediated immune responses to both LVS and Mtb.

That is briefly the personnel and what the personnel are doing. I just want to also briefly summarize our regulatory duties. We are providing a lot of preclinical guidance these days. A number of TB vaccines are in the preclinical stage. Especially, we are trying to provide guidance for

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investigators now. We, of course, review IND submissions; review BLAs; do inspections. We review product labeling and lot release review. We also assist in developing regulatory policy. Specifically, Dr. Brennan has been involved in developing policy for transgenic vaccines and I have been involved with developing policy for DNA vaccines.

In terms of regulated products, we mainly review vaccines, especially TB and malaria vaccines. As all of you probably know, these are two of the major international vaccine development pushes at the current time. We also review immunotherapeutics, including BCG which is mainly used as a therapeutic for bladder cancer in this country, and diagnostics, skin test reagents such

as tuberculins and coccidioidins, and we consult with the Center for Devices on review of devices, especially those involved with TB.

Just to prove that we are not all desk-bound bureaucrats, this lists some of the ways that we have been involved with the public health and scientific community. Mike Brennan actually spent six months on detail at the WHO working on TB vaccine issues. He is now involved with a number

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of WHO committees including WHO Clinical Trials Working Group for TB.

Our lab recently signed a contract to provide standard reagents for the WHO. What we will do is send these reagents out to anyone throughout the world who wants to do preclinical assays on TB vaccines. We have also been involved in CDC skin test studies. We are involved with the BTEP program which is a biotechnology exchange program. It essentially provides financial assistance and scientific expertise to the countries of the former Soviet Union.

Also, in terms of our involvement with the public health community and scientific community, we run a number of NIH study sections, blue ribbon panels. I am on the advisory committee for the elimination of TB, the federal TB task force, and I am on a number of editorial boards for scientific journals. That is a brief overview of what we do

in our lab at CBER.

DR. STEPHENS: Thank you very much,
Sheldon. Any questions for Dr. Morris?

[No response.]

Our last presentation in this session is
by Dr. Chumakov on the Laboratory of Method

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Development.

Overview of Laboratory of Method Development

DR. CHUMAKOV: Good afternoon. My name is
Dr. Chumakov and I am the Chief of the Laboratory
of Methods Development within the Division of Viral
Products.

The lab was originally created within the
Division of Product Quality Control. It was
organized by Dr. Inessa Levenbook. I think it was
in '91 and then it was moved to the Division of
Viral Products. When Dr. Levenbook retired Dr.
Asher moved from NIH and was the chief until the
lab was split in two parts. The part that was
doing mostly transmissible spongiform
encephalopathy studies was moved to the Office of
Blood and I was appointed as the chief of this lab.

When it was created the original goal was
mostly to create methods for refinement, reduction
and replacement of animal tests, primarily and
first exclusively for the oral polio vaccine. But
later as the work progressed and we achieved some
success in development of both molecular and animal

tests, the mission expanded and now we consider our mission as the development of cutting-edge techniques for evaluation of vaccines and probably

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other biologicals. We work closely with the World Health Organization to implement these methods in industry. We also have some bilateral contacts with industry for techniques developed in this lab.

So, I think that our work illustrates the unique role of CBER science because we are in a unique position to do some research on quality of biologics that cannot be done either in industry or in academia. One other important mission of our lab is to develop practical tests for a lot release program that is going on at CBER.

Our support, unfortunately, primarily comes from outside sources. I mean, in recent years about 80 percent of our funds were generated by grant supports from various places, starting with animal right groups to NIH and DRPA and the National Vaccine Program Office. In the handout you probably have a list of grants that we recently received. On average we would have about \$500,000 in our lab from outside sources.

The lab currently has 13 people. Five of them have FT positions and the rest are hired as post-doctoral fellows through a contract mechanism.

We have nine major projects. The first one that was originally the beginning of the lab is

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development of method mutant analysis by PCR restriction enzyme cleavage for evaluation of quality of oral polio vaccine. So, it was originally developed for type 3 OPV and the essence of the method is PCR-based quantification of mutants that determine mutant virulence of live virus.

Then we also created similar methods for type 1 and type 2 OPV. The method was evaluated by the World Health Organization Collaborative Study, and about two or three years ago was recommended by the Expert Committee on Biological Standardization as a routine mandatory test for lot release of oral polio vaccines as an individual method of choice.

So, we were very encouraged by this success and we decided to expand this concept to include other live viral vaccines, and started a project on evaluation of consistency of yellow fever virus production. It was done in collaboration with the Russian Institute of Poliomyelitis with Dr. Karganova. This is a vaccine manufacturer in Russia. They actually supplied us with high passage stocks of the virus that we studied on a molecular level and identified one mutation that we are currently studying as a

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potential marker for consistency in monitoring

yellow fever vaccine.

We also started a bunch of projects, because it is not just one product, on mumps virus vaccine live. It has been a controversial product because of the number of strains that were used for production of this vaccine were actually withdrawn from the market, including for instance the rubini strain that was withdrawn, a vaccine produced by SmithKline. On the other hand, some vaccine manufacturers are still successfully using this strain for vaccine production with no excessive adverse reactions.

So, we started a project and were successful in identifying molecular profiles of mutations in products that are acceptable and those that are unacceptable. So, currently we have ways of monitoring production of this vaccine and we can tell products made by different manufacturers, one from another.

Some work was done on the Jeryl Lynn strain currently used for manufacture of mumps vaccine in this country. So, for the first time we have identified complete nucleotide sequences of both components of this vaccine and have developed

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methods based on MAPREC and MALDI-TOF mass-spectrometry and microarray analysis for quantification of relative abundance of both components. That enables us to monitor consistency

of production of this vaccine because the ratio of the components depends on the conditions of vaccine production.

Another group of projects that are developed in our lab are focused around the new transgenic mouse model for evaluation of neurovirulence of oral polio vaccine. These mice were created in Japan and Columbia University. They express human receptor for polio virus. So, they can be successfully infected with polio virus and develop clinical poliomyelitis.

Dr. Dragunsky developed highly sensitive methods for evaluation of neurovirulence by intraspinal inoculation of these transgenic mice. You can observe them for clinical signs of paralysis and death, and can distinguish the ones that have excessive neurovirulence. So, again, it was evaluated by the World Health Organization and was recommended as a an in vivo method of choice, as a kind of replacement for the monkey neurovirulence tests in combination with MAPREC.

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About two years ago was the fiftieth anniversary of the World Health Organization and the Director of the Division of Biologics named MAPREC and the transgenic mouse model as the best developments in biologics in the last ten years. Both were developed in this lab so it gave me great pride.

The other outgrowth of this transgenic mouse project was the creation of new methods for evaluation of immunogenicity and protectivity of inactivated polio vaccines. So, it also was developed originally by Dr. Tafts in our lab and then Dr. Dragunsky built on his protocol and created a method for an immunization challenge test of vaccine prepared from other alternative strains. Currently, some manufacturers consider making the vaccine from the Sabin strain just because production of vaccine virulent strains can be dangerous after eradication of poliomyelitis.

This method works very well. There is a good correlation between immunogenicity of products made both from conventional strains and from Sabin strains, and protection of mice against the challenge with wild type strains.

One other project that is actually being

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developed by Dr. Rezapkin, who was also evaluated at this site visit, is the ELISA test for IPV and creation of immunological profiles. He managed to substantially improve the conventional ELISA test for potency of IPV and it was very important because at CBER, at this point, until now we had no routine method for potency testing of IPV and it was important since the country has switched completely from OPV to IPV.

But on top of that, Dr. Rezapkin also

created an entirely new approach to evaluation of IPV by measuring immunological profiles by using a uniform protocol that enables him to measure selective reactivity of vaccine by individual monoclonal antibodies. So, right now we can not only measure the potency of this vaccine but also quantitatively compare different batches for the profile of relative contribution of different epitopes into the overall immunogenicity.

Finally, there is a big group of methods that are being developed, and this group of projects is actually headed by Dr. Chizhikov who is considered for conversion as a principal investigator. It is based on oligonucleotide microarrays for identification and fine genotyping

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of viral and bacterial pathogens. So, his successes include creation of a very simple method for rapid genotyping of rotaviruses, orthopoxviruses, including smallpox and monkey pox. This project was supported both by DRPA and the Biotechnology Engagement Program, and it was done in collaboration with the Russian scientists at vector depository of smallpox virus. Then, it also included a few projects involving microbial pathogens, including factors of pathogenicity factors of E. coli, antibiotic resistance to Staphylococcus, and so on.

One other important project is

determination of point mutations in the vaccine-derived polio viruses that cause adverse reactions after OPV administration, and evaluation and rapid characterization of recombinant strains that can be done instantly. Unlike traditional methods that may take a few weeks or months to characterize the vaccine-derived strains, we can do it in a matter of a few hours.

One other sub-project of this microarray research is screening of reassortants of influenza B. We created a chip and this was done by Dr. Ivshina to instantly genotype all eight segments of

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influenza A virus. We can now sort through the reassortants strains that are created for vaccine development and select the appropriate strains for future vaccine development.

Lastly, we also are concerned about cell banks consistency issues, cell banks used for vaccine manufacture. So, we have started a project through gene expression profiles to characterize consistency of cell banks used for vaccine production.

Also, we are concerned about issues of stability of PrP gene because there was an idea expressed that PrP may mutate and perhaps jeopardize safety of vaccine produced in cell cultures that may contain mutant prion genes. So, we studied HeLa cell lines that are separated by

more than 700 passages and found no mutations, suggesting that this gene may be stable enough and perhaps does not present a major threat in this respect.

We also started an experiment in which we produced human neuroblastoma cell lines that express mutants characteristic for familial Creutzfeldt-Jakob disease and we plan to inoculate squirrel monkeys, the most sensitive species of

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monkeys, and see whether these mutants present any threat. Should some of these monkeys come down with this disease, it will be a positive proof of the prion hypothesis. On the other hand, if no monkeys develop any disease, then it will demonstrate that the threat from this process is probably minimal.

So, I mean, we have a diverse group of projects but they are united by our unique role in ensuring safety of biologics, and we hope that the methods that we develop can be used both by regulatory authorities and industry to improve the safety of vaccines.

DR. STEPHENS: Thank you, Dr. Chumakov.
Questions from the committee?

DR. PALESE: Peter Palese. I have one question. What is the proposed use of the HeLa cells in terms of vaccine production? I understand that the prion protein doesn't change but, I mean,

what about the papilloma virus sequences in there?

DR. CHUMAKOV: No, I probably did not make myself clear because we don't, and nobody else as far as I know, proposes to use HeLa cells for any production. The reason why we study HeLa cells is that this is perhaps the most extensively passaged

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cell culture so we wanted to have a cell culture that is available in the most distant lineages and see whether over 700 passages there may be some mutations accumulated. So, the HeLa cell experience demonstrated that even after passaging cell culture for 700 passages we don't see any mutations. So, basically the mutation rate is minimal and does not affect stability of PrP gene in HeLa cells. So, we hope that it can be extrapolated to other cell cultures that are actually used for production of vaccines.

DR. STEPHENS: Thank you. If there are no further questions, I think at this point I want to thank the speakers and move, Jody, to the open public hearing.

DR. SACHS: Thank you. As part of the FDA advisory committee meeting procedure, we hold open public hearings to give members of the public an opportunity to make a statement concerning matters pending before the committee. Mr. Chairman, at this time I have not received any requests to speak in today's open public hearing. Is there anyone in

this room who would like to address the committee at this time? I see no response. At this time I would like to close the open public hearing and

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turn the meeting back over to you, Dr. Stephens.

DR. STEPHENS: Thank you. I think we will move quickly to our closed session and hear from Rich Whitley about the site visit report on the Laboratory of Mycobacterial Diseases and Cellular Immunology. Rich?

DR. SACHS: Excuse me, can I just hold the meeting for one second? At this point of the meeting we need to close the meeting. So, I need just about thirty seconds because there are people that need to leave the room.

DR. WHITLEY: Just tell me when you are ready.

DR. PALESE: Could I just ask, I had a question regarding the last teleconference on March 18th, and I think it is a question for the closed session. Can I ask you that at the beginning or the end of our closed session?

DR. STEPHENS: Why don't you wait until the end of the closed session and we will deal with that question?

[Whereupon, at 2:30 p.m., the proceedings of the open session were adjourned, to reconvene immediately in closed session.] □