FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE MEETING

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OPEN SESSION

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WEDNESDAY,
NOVEMBER 14, 2007

The Committee convened at 1:00 p.m. in Conference Rooms A and B of Building 29B of the National Institutes of Health, Bethesda, Maryland, Ruth A. Karron, M.D., Chair, presiding.

COMMITTEE MEMBERS PRESENT:
(All members present via teleconference)

RUTH A. KARRON, M.D., Chair
MONICA M. FARLEY, M.D.
PHILIP S. LaRUSSA, M.D.
STEVEN SELF, Ph.D.
BONNIE WORD, M.D.
JOHN MODLIN, M.D.
SETH HETHERINGTON, M.D.
(Non-Voting Industry Representative)
LISA JACKSON, M.D., M.P.H.
JACK STAPLETON, M.D.

EXECUTIVE SECRETARY PRESENT:

CHRISTINE WALSH, R.N.

COMMITTEE MANAGEMENT SPECIALIST PRESENT:

DENISE ROYSTER

ALSO PRESENT:

NORMAN BAYLOR, Ph.D.
MILAN BLAKE, Ph.D.
MICHAEL J. BRENNAN, Ph.D.
KONSTANTIN CHUMAKOV, Ph.D.
WILLIAM FREAS, Ph.D.
JAYA GHOSH
SHELDON MORRIS Ph.D.
JAY SLATER, M.D.
JERRY WEIR, Ph.D.
WAYNE WRAY, Ph.D.

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P-R-O-C-E-E-D-I-N-G-S

1:01 p.m.

CHAIR KARRON: Yes, I would like to call to order the last VRBPAC meeting of 2007. Welcome, everybody. And we are here today to discuss site visit reports for two laboratories. And, Christine, at this point, I'm going to turn the meeting over to you.

DR. WALSH: Okay. I'm just looking, I'm sorry, I'm looking for something. I'll be right with you.

CHAIR KARRON: Okay.

DR. WALSH: No, I'm missing my conflict of interest. Denise, my conflict of interest? Just give me your copy. I don't know what happened to it. Thank you. I'm sorry, I'm back.

Good afternoon, I'm Christine Walsh, the Executive Secretary for today's teleconference meeting of the Vaccines and Related Biological Products Advisory Committee meeting. I would like to welcome all of you

to this meeting of the Advisory Committee.

There is a speaker phone for public participation located here in Building 29B, Conference Room A/B on the NIH campus. This afternoon's teleconference meeting will consist of sessions dealing with the presentations and Committee discussions that are both open and closed to the public, as described in the Federal Register notice of October 23, 2007.

At this time, I would like to introduce the Committee Members and ask that you acknowledge by saying present if you can hear me. The Committee Chair, Dr. Ruth Karron, Professor, Johns Hopkins School of Hygiene and Public Health.

CHAIR KARRON: Present.

DR. WALSH: Dr. Monica Farley, Professor of Medicine, Emory University School of Medicine.

Dr. Philip LaRussa, Professor of Clinical Pediatrics, Columbia University.

DR. LaRUSSA: Present.

DR. WALSH: Dr. Steven Self, Professor, Department of Biostatistics, University of Washington, Fred Hutchinson Cancer Research Center.

DR. SELF: Present.

DR. WALSH: Hi, this is Christine, who just joined us?

DR. FARLEY: It's Monica Farley. I'm sorry I'm calling in late.

DR. WALSH: That's okay, Dr. Farley, we're just going over roll call. I just did your name. Welcome.

DR. FARLEY: Thank you.

DR. WALSH: Dr. Bonnie Word, Assistant Professor of Pediatrics, Baylor College of Medicine.

DR. WORD: I'm present.

DR. WALSH: Dr. Seth Hetherington, Industry Representative, Senior Vice President, Clinical and Regulatory Affairs, Icagen Incorporated.

DR. HETHERINGTON: Present.

DR. WALSH: Dr. John Modlin, Professor of Pediatrics, Dartmouth-Hitchcock Medical Center.

DR. MODLIN: Here.

DR. WALSH: Dr. Lisa Jackson, Senior Scientific Investigator, Group Health Cooperative, Seattle, Washington. Dr. Jackson did inform me that she may just be a little late in joining the teleconference this afternoon.

Dr. Jack Stapleton, Professor of Infectious Diseases, University of Iowa Hospital Clinic.

DR. STAPLETON: Present.

DR. WALSH: Thank you. I would like to thank all Committee Members for taking the time to join us today. I would also like to note at this time that this will be the final VRBPAC meeting for our Chair, Dr. Karron, along with Members Dr. Self, Dr. Farley, Dr. Word, and Dr. LaRussa. We wish to

thank each of you immensely for your dedication and valuable contribution to the VRBPAC Committee over the past several years.

Now, I would like to introduce some of the staff members that will be participating in today's meeting and are currently seated in the room. Dr. Norman Baylor.

UNIDENTIFIED SPEAKER: He just walked out.

DR. WALSH: Okay. Director, Office of Vaccines Research and Review. Dr. Michael Brennan, Associate Director for Research. Dr. Jerry Weir, Director, Division of Viral Products. Dr. Milan Blake, Acting Director, Division of Bacterial, Parasitic and Allergenic Products. Dr. Konstantin Chumakov, Chief Laboratory Methods Development, Division of Viral Products. And Dr. Sheldon Morris, Chief Laboratory of Mycobacterial Diseases and Cellular Immunology, Division of Bacterial, Parasitic and Allergenic Products.

I ask that all our Committee Members identify yourselves each time you speak. We have a transcriber present who will need your assistance in order to accurately transcribe all comments to the appropriate Committee Member. I also ask that our Committee Members not use cellular phones, since they may add extra unnecessary background noise to the line.

Should during the teleconference a source of noise occur in your office, we would appreciate it if you would use the mute button on your phone, if you have that option. We ask that you do not place us on hold, since many clinical centers have background music and that could be distracting to those remaining on the teleconference line.

I would now like to read into the public record the conflict of interest statement for this meeting.

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 Members of the Committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Advisory Committee's compliance with federal conflict of interest laws, including, but not limited to 18 USC 208, is being provided to participants in today's 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. Under 18 USC 208, applicable to all government agencies, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it

is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Today's agenda includes updates of the research programs in (1) The Laboratory of Method Development, Division of Viral Products and (2) The Laboratory of Mycobacterial Diseases and Cellular Immunology, Division of Bacterial, Parasitic and Allergenic Products, Office of Vaccines Research and Review, CBER.

Based on the agenda, it has been determined that the Committee discussion present no actual or appearance of a conflict for today's meeting. Dr. Seth Hetherington is serving as the industry representative acting on behalf of all related industry and is employed by Inhibitex Incorporated.

Industry representatives are not special government employees and do not vote. This conflict of interest statement will be available for review at the registration

table. We would like to remind Members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

That ends the conflict of interest statement. Can I just ask who recently joined us on the line?

DR. JACKSON: Lisa Jackson.

DR. WALSH: Hi, Dr. Jackson, thank you.

Dr. Karron, I turn the meeting over to you.

CHAIR KARRON: Thank you, Christine. Welcome again, everyone, to our

last meeting of 2007. Our first speaker will be Dr. Michael Brennan. Dr. Brennan, I see that you have two presentations and my thought, if it's okay with you, is for you to give both of those presentations and then for us to take any questions that we have at the end of that time.

DR. BRENNAN: Okay. That's fine.

CHAIR KARRON: Okay.

DR. BRENNAN: Yes. Okay. Well, welcome, everybody, good afternoon and thank you for participating in this extramural review of our two laboratory programs that are the focus of today's meeting.

I will start first giving the Center for Biologics Evaluation and Research talk, which is the hard copy program that says that at the top and says that it's a site visit introduction by myself for Kathy Carbone, who departed CBER last week. My intent for both of these talks is to be brief because I believe the focus of today's meeting

should be on the presentations by the Laboratory Chiefs of the two laboratories as well as the review by the VRBPAC Committee Members.

So the second slide then introduces the researcher/reviewer model, which most of you on the Committee know is the model that CBER uses where they have active scientists and laboratory also involved in review that form part of the team, along with regulatory scientists and clinical review scientists to perform regulatory responsibilities. The two laboratories today that are under review are active in this researcher/reviewer model and have active scientific programs, as well as regulatory responsibilities.

Slide three is just an organizational chart of CBER. It shows down at the bottom a number of the offices within CBER. Four of these have researcher/reviewer programs, including the Office of Biostatistics and Epidemiology, the Office of

Blood Research and Review, the Office of Cellular Tissue and Gene Therapies, and the office which is the focus today of Vaccine Research and Review.

On the fourth slide, I'm going to just spend a few slides just giving a brief overview of the site visit and extramural review process.

So in the evaluation of our research programs, we have both an internal and external management evaluation program. The internal management review looks at the yearly accomplishments that are tabulated for each of the research programs, which include publications, participation in regulatory policy, the development of guidance documents, the involvement of these researchers in presentations of their research and their outreach activities. And they are evaluated within the office, in this case, the Office of Vaccines.

There is also an external review

process, which is done through the VRBPAC Committee and why we're here today, and that's done on a four year cycle for each laboratory.

On the next slide, there are extramural review guidelines. As you know, for the site visit team, which provides a criteria for evaluating each program and it occurs through each cycle, there should be an evaluation of the last four years of progress of the research teams. The proposals contain research activities proposed for the next four years by the program and each of those is evaluated for relevance to the regulatory mission, for its management structure, for its originality and innovation, and for its quality, both of the program and of the investigators involved in the research program.

The regulatory activities and the regulatory work by the laboratory are not assessed as part of this extramural review. It is focused on the research.

And the next slide called Site Visit Team and suggestions to get are continue on the right track. These are the sort of nitty-gritty things that the site visit team is asked to do, which is evaluate the quality of the science, propose new research directions and approaches to be considered, identify gaps or needs in laboratory expertise, and comment on changes in the laboratory organization or on new collaborations.

And the next slide, in the process of the site visit itself, there is an oral summary that is presented at the end of the review and then there is a written report, which is also prepared, which comments on each investigator on the laboratory program on management issues, as well as on any specific personnel issues.

And the next slide, as is happening today, this draft report has been distributed to the full Advisory Committee. There has

been a final report which is approved and that's why we're here today by the Advisory Committee. And this final report then is used for research evaluation by both the offices and by CBER for decision-making on the programs, including funding and FTEs, laboratory space, et cetera, and also for evaluation by the PCE Committee on individual personnel actions.

So that's my introduction to CBER. I think I'm much quicker than Kathy. I'm sorry for that. So I'll proceed right into a brief overview of the research program within the Office of Vaccines. And you have that on a separate tablet there of vaccine presentations.

DR. WALSH: Excuse me, this is Christine. Who joined us? Okay. Continue, Mike.

DR. BRENNAN: Okay. If you have that slide presentation called the Office of Vaccines Research and Review with my name on

the cover, if you go to the second slide, that's an organizational chart of the Office of Vaccines. We have two product divisions where the researcher/reviewer model is used, that's the Division of Bacterial, Parasitic and Allergenic Products and the Division of Viral Products. Norman Baylor is the Director. He is here with us today, if you have any questions for him.

We have -- the two programs today, one is in the Laboratory of Mycobacterial Diseases and Cellular Immunology is within the Division of Bacterial, Parasitic and Allergenic Products and the other Laboratory of Methods Development is within the Division of Viral Products. And Dr. Blake and Dr. Weir will talk a little bit about a brief overview of those divisions.

And the next slide, just briefly, the mission of the Office of Vaccines it's major regulatory responsibilities include the review, evaluation, and taking appropriate

action on investigational new product submissions, on licensing submissions, and on amendments and supplements and major regulatory responsibilities.

But we also have major research responsibilities to plan and conduct research related to the development, manufacture, and testing of vaccines and other products that we regulate, such as allergenics. And then we have other regulatory responsibilities which include the development of policy and procedures such as guidance documents and standards that are related to our products, evaluation and testing of licensed vaccines which occurs now in a focus through our new Division of Product Quality, evaluate and monitor clinical experience and adverse events that we do in collaboration with the other Office of Biostatistics and Epidemiology.

Our staff participates in inspections of manufacturing facilities for the evaluation of good manufacturing practices

and we also have a number of outreach activities, including with other national regulatory authorities in other countries. There is good examples in both laboratories today of outreach activities internationally with tuberculosis and with polio issues.

And the next slide of major OVRR research priorities, some of you know we have established a new management process and we have -- we are focusing now on developing new priorities each year that should -- that our research programs should address. We have four this year.

The first one is focused on the safety of vaccines and related products. The second one on evaluating the effectiveness of vaccines and other biologics. The third one is to facilitate the development of products that address new public health threats and emerging diseases. And the last one is to develop and evaluate novel scientific technologies that assist in the regulatory of

biologics and any evaluation of the quality of the products that we regulate.

And the next slide, this is just a brief overview of how we are evaluating our office research programs. We have an annual-- on an annual basis, we evaluate all of the programs within the office that this process now is under a new management system, which we discussed with the VRBPAC earlier this year, and we are on track to have further discussions of this in the spring of 2008.

And it begins within the divisions. The programs are evaluated within the divisional management and then through the office management for various criteria, including regulatory relevance and how it is addressing emerging issues, what it's proposing to do in the future, and budget decisions are made on -- after this evaluation.

Just as important is the extramural review, which is the process we are involved

in today, where individual programs are evaluated by the VRBPAC Committee. And together these evaluations and criteria are taken forward to the PCE Committee that is used by CBER for promotions and conversions.

And the next slide is a summary slide just to say the main purposes then of our research program within the Office of Vaccines, does the research regulatory staff support the science-based review and regulation of vaccines, so the science is here to be relevant to the regulatory mission of the FDA.

Secondly, the research priorities focus upon our mandate to assure the safety and purity/potency and efficacy of vaccines and other biologics. And lastly, our research program also serves to recruit, train, and retain highly qualified scientists.

And lastly, just thank you very much for your time and effort. And if you have any questions for me either about the

CBER or the office program, I'll try to answer those.

CHAIR KARRON: Thank you, Dr. Brennan. Are there any questions for Dr. Brennan? Okay. Thank you. Our next presenter will be Dr. Jerry Weir, who will give us an overview of the Division of Viral Products.

DR. WEIR: Good afternoon. Thank you, everyone, for participating. I'm going to try to be even more brief than Mike was, so that we can move on to the lab presentation.

The first slide on your handout shows the organizational chart for the Division of Viral Products. There are seven laboratories in this division listed here: Laboratory of Hepatitis Viruses; the Laboratory of DNA Viruses; the Laboratory of Respiratory Viral Diseases; the Laboratory of Immunoregulation; the Laboratory of Vector-Borne Viral Diseases; the Laboratory of Retroviruses; and the subject of today's or

part of today's discussion, the Laboratory of Method Development with Konstantin Chumakov as Laboratory Chief.

The second slide shows the brief distilled mission and functions of the Division of Viral Products. Essentially, it can be divided into two areas. We regulate viral vaccines and related biological products, ensure their safety and efficacy for human use and we also facilitate the development, evaluation and licensure of new viral vaccines that positively impact the public health.

The next slide. There are a lot of activities that we participate in in support of this mission. They are listed here, some of which were already touched upon by Mike in the previous presentation. We review Investigational New Drug applications. We review and act on Biologic License applications and their supplements. We are involved in lot release review and some

testing.

We participate in post-marketing activities. An example would be any sort of product deviations to our licensed products. We participate in manufacturer inspections. And as already mentioned, we have a very large role, consultation role with other public health agencies, such as WHO, CDC, NIBSC. And last, but not least, we maintain a research program, and those research activities in our division are related to the development, manufacturing, and testing of viral vaccines.

The type of research projects that we have vary anywhere from extremely basic to very applied. They can include aspects of viral pathogenesis, vaccine safety and efficacy, including cell substrates, vaccine and viral vector evaluation, studies on the correlates of protection that we need to evaluate new vaccines, reagent preparation, methods development evaluation and, of course, we address emerging issues, for example BSE,

counter-terrorism, pandemic influenza in the last few years.

The subject of today's site visit report in the Division of Viral Products centers on the Laboratory of Method Development. This site visit was conducted on March 15th of this year. And in the next to the last slide I have listed the teams that were evaluated. There are three teams in this laboratory.

The first one with Konstantin Chumakov, who is the Chief of the Laboratory, is the head of this team. They focus on the evaluation of safety and potency of viral vaccines based on molecular consistency.

A second team is headed by Vladimir Chizhikov. Their focus is on the microarray-based evaluation of purity and safety of biological products.

And the third team is led by Steven Rubin, who is an acting team leader at this point, and the focus of this team is

developing tests to evaluate virus vaccine safety for the nervous system.

And in the last slide, I briefly listed some of the major regulatory responsibilities and areas of research. The regulatory responsibilities of this laboratory include the regulation of polio virus vaccines, measles, mumps, rubella virus vaccine. We address mycoplasma vaccine issues, and also we have -- this laboratory has, responsibility for various other viral vaccines, which include parvovirus, varicella virus vaccine, Ebola and some influenza work.

The areas of research are pretty varied as you will hear in just a minute, but some of the areas that they focus on include the development of new methods to assess the consistency of viral vaccines, the development of preclinical neurotoxicity assays for assuring the safety of live virus vaccines, the development of methods for rapid accurate identification of biological agents,

evaluation of surrogate endpoints for vaccine safety, and the development of methods to detect extraneous agents in vaccines.

And that's all I have for my intro. If anyone has any questions, I'll try to answer them.

CHAIR KARRON: Thank you. Questions for Dr. Weir? Okay. Dr. Chumakov, I think we will move on to your presentation.

DR. CHUMAKOV: Well, thank you. Good afternoon. This Laboratory of Method Development was created in early '90s within the Division of Product Quality Control in the Office of Establishment, Licensure, and Product Surveillance. And after departure of Dr. Leyvandook, who was the founder of the lab, the lab was translocated to the Division of Viral Products because we primarily deal with issues of a viral nature.

So the -- our mission is to create new methods to -- for quality control and for pre-license evaluation of new viral vaccines.

And we like to think of ourselves not as just developing new methods, but rather trying to come up with new approaches for evaluation of biologics. And I will give you later a few examples of such development.

So I move to Slide No. 3. And we have three research teams led by three principal investigators, myself, Dr. Chizhikov, who is reviewed for the first time as an independent PI because during the last site visit four years ago, he was recommended for conversion as a senior investigator, and this was not really done, just because of his citizenship status. So after four years, he was reviewed again this time and according to the recommendations, he was presenting his data as a PI.

And then Mr. Rubin, who is an acting PI. He inherited this group from Dr. Carbone, who recently departed CBER. And therefore, he presented at the site visit also independently.

So my group primarily deals with issues of viral vaccines, and we focus on the analysis of the actual substance of viral -- live vaccines and inactivated vaccines.

Dr. Chizhikov's focus is primarily on the technological development in the field of microarray research with a particular focus on purity of vaccines analysis of -- and trying to find adventitious agents with, again, a primary focus of mycoplasma detection and classification.

And the third group is primarily-- it's called neurotoxicity group, because its primary focus is on development of new methods for analysis of neurotoxicity of different vaccines.

So we have on the fourth slide list the staff of the Laboratory of Method Development. In the past year, we have three departures, Dr. Carbone, who left, and also two post-doctoral fellows in my group also left during this period.

Our regulatory responsibilities include polio vaccines and combination products with IPV, mumps, measles, rubella and varicella vaccines. We also perform lot release of IPV, MMR and HPV vaccines. We perform quality control of vaccines that are under licensure, and we also deal with review of INDs and BLAs related to these products.

We also are involved in international activities, and three of us are advisors to the WHO. We are also involved in the creation of international guidances and WHO recommendations. We collaborate with WHO on validation of reference materials and participate in international collaborative studies, and also we are involved in the activity under the DHHS Biotechnology Engagement Program.

So I move to Slide No. 7. And I will start in reverse order, and I will first describe the scope of research activities and accomplishments in the neuropathogenesis team

led by Steven Rubin. So they perform research and development of new methods for analysis of neurovirulence of vaccines, primarily mumps vaccine. Historically, this group started with creation of rat, newborn rat method for evaluation of residual and neurovirulence of mumps vaccine live.

And recently, they diversified and also began development of methods also based on rat model to assess neurovirulence potential of influenza vaccines and smallpox vaccines. So there was a number of new models developed within this group, including the newborn rat test. And they also are involved in the development of -- in studies of molecular determinants of neurovirulence, and particularly in mumps virus by doing some molecular studies.

So basically, after departure of Dr. Carbone, this group remains perhaps the leader within CBER on issues of neuropathogenesis for viral vaccines. And

since mumps is not really something that is studied widely in this country, so this lab is the only -- is the second of two labs in the United States that deal with mumps issues.

So their research accomplishment in mumps, and I move to Slide No. 9, include development of rat model for assessment of residual neurovirulence of this vaccine, and this test is now undergoing WHO collaborative study to evaluate utility of this method. They also created a method for analysis of neurovirulence in cell culture.

They created a model of reverse genetics where they can manipulate genome of mumps virus, both wild type and attenuated vaccine virus in order to study the effect of individual genes on the neurotoxicity of the virus.

They recently, in 2006 and early 2007, were involved in collaboration with CDC in outbreak investigation. As many of you know, there was an outbreak of mumps in this

country, first since the B- perhaps in 20 years, and Steve Rubin was actively involved in this investigation.

So now, Slide No. 10. He has also initiated projects on development of methods for analysis of influenza virus neurovirulence and vaccinia virus neurovirulence, and this is very much a work in progress, and it's very important considering that there is a number of new influenza vaccines are on the horizon, and CBER feels that we need to have an active program to address this issue, because, I mean, this is something that was not really very much on the radar screen before. So this is something that we feel needs to be advanced.

Let me move to the second research team led by Dr. Chizhikov. As I already mentioned, he was -- before he was a part of my lab, he first came in 1998 as a post-doctoral fellow, and then he established himself as a leader in microarray research.

And in the last four years, he was functioning independently, so we tried to separate/segregate our research priorities in such a way that he could become an independent principal investigator as was recommended by our previous site visit. So he has a very small team. He only has two post-doctoral fellows.

And his research focuses on two major subjects. First is development and improvement of microarray technology. He is -- came as by his education, so he is very active in collaborating with other teams in bringing new technical ideas to CBER to improve in this approach. But his focus on the biological aspects of microarray studies is primarily on safety and purity. And in the past two years, he was working primarily on mycoplasma detection and identification methods.

So the technical approach, as I move to Slide No. 13, it's a use of advanced

microarray substrates and instruments. He also pioneered in using nanotechnology, nano-gold particles that significantly increase sensitivity of this method and also enabled him to do visual analysis of the results without the need for expensive equipment.

He also is involved in collaborations with CDRH, another center within the FDA on the so-called Lab-on-Chip. It will be an integrated instrument that would perform all steps of this analysis in one -- on one slide.

Biological models that he investigated included drug-resistant TB, genotyping of measles isolates and this was done in collaboration with the Johns Hopkins University. He also collaborated with CDC on genotyping of VZV isolates and also analysis of vaccine strains isolated at CDC.

He also created a method for genotyping of rotaviruses, and this work was also done in collaboration with NIH. And he

also plans to transfer this method to CDC. He also collaborates within CBER with the Office of Blood Research and Review on use of his approaches for detection of pathogens in blood.

And finally, his other -B his other studies are in collaboration with the Center for Food Safety at the FDA on detection and classification of food-borne pathogens, listeria and E. coli.

Next slide lists his accomplishment and primarily this is in the mycoplasma part of his project. So he established a comprehensive collection of mycoplasma species that were ever found in biological preparations, he created an extensive database collected from all over the world and also developed in-house a nucleotide sequence database of ribosomal RNA that enabled him to create a microchip that can discriminate between any of the above mycoplasma species.

And he also recently came up with

the idea of enrichment of mycoplasma on cell culture. And this is a very significant development because new techniques including PCR and microarray analysis in principle are incapable of being as sensitive as the traditional microbiological methods just by virtue of using a very small sample volume.

So his proposal allowed him to kind of combine both high sensitivity of microbiological methods and a rapid nature of new molecular techniques and a very high resolution. Basically, he can -- he shortened the time needed for analysis from 21 days to just one week. And as a result, he can accurately identify mycoplasma contamination that is present in cell cultures and other biological materials.

He is quite productive over the past four years. He published 24 papers and applied for two patents. And he presented to numerous international meetings, including oral presentations as an invited speaker.

So finally, let me move to my program, and Slide No. 16 lists staff that works with me. As I already mentioned, the last -- in the last year, Dr. Ivanov and Dr. Cherkasova left my group, so now we are down to six people in my lab. And the principal directions in Slide No. 17 include studies of oral polio vaccine, inactivated polio vaccine, and we also study recombinant and flavivirus vaccine. They are under development at the National Institute of Allergy and Infectious Diseases here at NIH.

We also do some influenza research on influenza vaccines. We also use microarray methods for genotyping of orthopox viruses and herpes viruses. And this is historical, and this project was done as a part of our BTEP collaboration with former Soviet Union scientists.

And we also are conducting research in molecular consistency of cell substrates. In this particular case, it's analysis of

tumorogenicity of Vero cells.

So first, oral polio vaccines. So our lab pioneered in using of transgenic mice for -- as a substitute for the mouse -- for the monkey in neurovirulence test for oral polio vaccine, and it was evaluated by the World Health Organization and about four years ago was recommended as a kind of alternative method for assessment of neurovirulence of -- and lot release of oral polio vaccines.

So now, WHO initiated a process by which they will eliminate monkeys as a recommended method because the previous recommendation was to have monkeys as a golden standard and mice were an alternative. So now, they want to make transgenic mice developed by Dr. Dragunsky in my lab as a primary tool for assessment of neurovirulence in lot release of oral polio vaccine.

And we are involved in this international collaboration to make this happen. So we also study molecular basis of

neurovirulence and interactions of polio virus with innate immune system, and we have published and -- so this is all done, I mean, this part is done in collaborative efforts with the University of Chicago and with the Cleveland Clinic Foundation.

So our main emphasis in OPV is on development of method that could enable analysis of clinical studies, because recently there was a number of studies conducted with IPV and OPV and interpretation of these studies are complicated, because of the inability to study both immune response and genetic stability of OPV.

For instance, one example was that it was suggested that prior immunization with IPV makes OPV more genetically unstable. And this issue was unresolved for the past 10 years. So we have developed ex vivo molecular technique that enabled us to directly amplify full lengths genome of polio virus directly from stool samples.

And by using this method, we have demonstrated as first there is no influence of prior immunization status on genetic stability of OPV. And second, we have found that immunization with IPV protected a significant part of vaccine recipients from being reinfected with OPV, suggesting that IPV elicits, after two immunizations, measurable intestinal immunity, which was important for understanding of the benefits that IPV can provide to vaccine recipients.

So we also studied adverse reactions caused by oral polio vaccine, and we performed a number of studies on the so-called vaccine-derived polio viruses. So we have discovered the recombination patterns that different polio virus serotypes are involved in and provided an explanation for the driving forces behind this recombination.

And we also published a study on antigenic drift that occurs in vaccine-derived polio viruses. So basically, the conclusion

was that vaccine-derived polio viruses very often revert at the antigenic sites. But despite this fact, they do not escape from neutralization properties and still -- so they do not present a threat of a runaway nature. So basically, we explained the driving forces behind such evolution, but we also demonstrated that these viruses do not present a threat in terms of being -- rendering a vaccine immunization ineffective.

So we also have a group of -- a number of publications on creation of advanced immunochemical procedures. First, we developed this, what we call, block-ELISA procedure that enabled us to very accurately measure potency of vaccine. And this is -- I mean, in my estimation, this is the best protocol for D antigen potency testing that exists so far.

And we also proposed a new approach for characterization and consistency monitoring of IPV by what we call epitope

profiling. And in short it means that we can quantify contribution of individual epitopes to the overall antigenicity of IPV. And recently, we also created a method that we call paratope profiling, basically meaning that we now can quantify contribution of individual immunoglobulins that are specific to individual epitopes.

So these two methods are -- the first method, epitope profiling enabled us to comparatively evaluate conventional IPV and Sabin IPV that was recently proposed, and we have demonstrated that Sabin IPV significantly differs from the conventional product.

And the paratope profiling also led us to discover that immunization with IPV and OPV produces very different profiles of antibodies. So our studies on activated polio vaccine also involve, as I already mentioned, evaluation of the new Sabin IPV. And this is Slide No. 20.

So this is done by using transgenic

mouse immunization challenge test that was also developed in our lab. And we also -- by using this method, we have found that wild Sabin IPV of Type I is equally or perhaps even more immunogenic and protective as the conventional product. Sabin IPV of Type II and III are less immunogenic and need further development.

We also explored the potential effect of novel adjuvants and, in particular, we used dihydroxy vitamin D3 and found that it not only increases secretion of local IgA in the mucosal surfaces, but also significantly boosts neutralization titer in mice immunized with IPV with this adjuvant.

And we also recently started a project on exploring the effect of alternative routes of IPV administration. In this particular case, we used this BioJet device. It's an air gun that delivers a vaccine directly into the skin. We found that it is significantly more efficient for inducing

immune response, and immune response was about 5 times greater compared to the subcutaneous and other routes of administration.

And this is very important because, apparently, this device is considered as a method for delivery of vaccines, especially in the developing countries in order to save cost of vaccine, because it can enable potentially a reduction of dose needed for immunization. And our studies they lend support to this idea.

So finally, let me move to other models that we work on, and this flavivirus project, it was -- it is supported in part by our interagency collaboration that we entered last year with the National Institute of Allergy and Infectious Diseases. And it is not only supported by this agreement with NIH, but also conducted in collaboration with a group in the Laboratory of Infectious Diseases at NIH that developed this vaccine.

So this vaccine represents a

chimera between West Nile and dengue virus, and it was demonstrated to be highly attenuated. But significant issues remain whether this vaccine is genetically stable and can -- if it can revert upon passage upon growth in the cell culture, during manufacture or in vaccine recipients.

So we have developed microarray analysis to study genetic stability. We have validated this technique and currently are studying experimental samples that we hope will enable us to address this issue. And the outcome will be a method for quality control and consistency monitoring of production of this vaccine.

So we also worked on seasonal influenza vaccine creation by developing microarray methods for genotyping of individual segments of both influenza A and influenza B. And the issue was that we wanted to create a method to be able to rapidly genotype reassortants that are created every

year for seasonal influenza vaccines.

So we have published this before for influenza B, and now we are working on influenza A, and the major accomplishments here include our ability now to amplify genomes of all influenza A viruses in 1 2, which was very problematic before. And we also created a number of oligoprobe that enabled us to discriminate between different segments from different strains. So we hope that this could be a useful tool in annual activity for creation of vaccine strains.

So finally, just briefly about the project I already mentioned. It was a genotyping of orthopox viruses and herpeses virus. So first, it was our DARPA-funded project and when we were exploring utility of microarrays for different applications in virology, and then it was picked up by Biotechnology Engagement Program and it was done in collaboration with Russian scientists.

And the reason for this was that

they are the only group besides CDC that have access to variola virus. So it was done in collaboration with two institutions in Russia. Now, this collaboration is over, but it resulted in several publications, so that's why I presented this at the site visit.

And finally, the last project is a molecular consistency on cell substrates. Vero cells, of course, are widely used for production of vaccines. First, it was killed vaccines, inactivated vaccines and now live vaccines. So issues of tumorogenicity still remain unresolved, because high passage Vero cells and Vero cells passage or prepared cell banks prepared in inappropriate conditions could potentially increase tumorogenicity, which is undesirable.

So our approach involves analysis of mitochondrial DNA and also use of microarray gene expression profiles to identify markers of tumorogenicity. And we also use proteomics approaches, too. And the

idea is that we want to identify molecular markers that would enable us to screen cell banks and to identify cells with potentially altered tumorogenicity properties.

So the same method, if we develop this approach into a workable method, we could also potentially use for analysis of consistency of cell substrates at the level of cell culture confluency and their metabolic status. So basically, this covers the scope of our stud,ies and in the future we probably will try to consolidate some of the projects because, I mean, this lab is 18 years old and as often happens we diversified perhaps in too many areas.

And with the departure of people and with limited resources, we probably will not be able to sustain the scope that we had before. And we will perhaps concentrate on the -- in the areas that we are most -- can be most helpful. And this includes some expertise in the polio vaccines and perhaps in

-- we will finish influenza viruses, but primarily focus on issues that we feel are -- we have maximum experience in.

So with this, I will finish and hope I didn't use too much extra time.

CHAIR KARRON: No. Thank you very much, Dr. Chumakov, for that very comprehensive presentation. Are there questions for Dr. Chumakov?

Dr. Chumakov, can you just say a little bit more about your very last comment about your -- that you think primarily for the future you will focus on polio and influenza? Will you continue to do some of the microarray work as well, do you imagine, in the service of that or will that be less of a focus of your laboratory?

DR. CHUMAKOV: Yes, we will use microarray methods, but before we B- in fact, I think we, in many areas, we were the first to use this approach for analysis, in the version that we used. So in the future

perhaps we will use it, but we will not -- I don't anticipate that we will be developing novel versions of this technique.

Not only because Dr. Chizhikov in my lab will focus on this, but it will be just one of the many other approaches that we will use.

So I mean, I really recently became more excited about immunological approaches that really this project is going extremely well. And now with this development of new paratope profile method, I think it has an extremely important future, not only in polio vaccines, because if we will be able to validate this approach in polio vaccine, we could do it for any other vaccine.

I think I'm very excited about this opportunity and probably I would -- I mean, at least mentally I am more prepared to diversify in this direction and willing to cut off some of the less important things that perhaps others could do.

CHAIR KARRON: Okay. Thank you. Other questions for Dr. Chumakov? Okay. Thank you. Hearing none, I think we will proceed to hear from Dr. Blake.

DR. BLAKE: Hi. First of all, I would like to extend to the Committee my thanks for your time and effort during this process. I just want to give you a little background into the Division of Bacterial, Parasitic and Allergenic Products kind of to give you an idea how Dr. Morris's lab sits in our division.

We have currently six laboratories that are in research, and they really are based on products and potential products into the future. Those of the allergenics is led by my Acting Deputy Director, Jay Slater, and that's the Laboratory of Immunobiochemistry.

The Enterics and Sexually Transmitted Diseases Laboratory is headed up by Dennis Kopecko, that of bacterial polysaccharides, i.e., that's the capsular

polysaccharides and conjugates are headed up by Willie Vann. Those that are specialized in respiratory and special pathogens, specifically many of those pathogens that use toxins or toxic compounds, are headed up by Drusilla Burns, and she is also now Acting Chief of the Laboratory of Methods Development and Quality Control.

And that brings us to the Laboratory of Mycobacterial Diseases and Cellular Immunology that is headed up by Sheldon Morris. And much as you have heard from Dr. Brennan and also Dr. Weir, if you look at our second slide, we have the responsibilities of the researcher/reviewer is to conduct regulatory review, also conduct very Critical Path sorts of research, both of the programs and special tasks. We also have -- serve as outside organizations as recognized by the subject matter experts WHO, PAHO and so forth.

The third, some of the work where

this becomes synergistic both the review and laboratory work, we do provide reagents and standards to worldwide and international. We do collaborative efforts for assay development. We try to improve the technology and do troubleshooting for both manufacturing in these assays. And also the research that we have, we gain expertise in to better anticipate issues and identify and fill knowledge gaps. We provide expertise and input into the vaccine community and provide guidance, advice to the industry.

The next slide, obviously, this is a slide that we -- this comes from our research priorities that is coming from the office, and I won't review these, but these are our priority as well, both safety, effectiveness, facilitating new biological products for health threats, and to develop new ways to increase the availability and quality of vaccines that we do regulate.

And that comes to the Laboratory of

Mycobacterial Diseases and Cellular Immunology that is headed up by Dr. Morris. There is three particular sections within this laboratory. One is headed up by Sheldon Morris, the second one by Michael Brennan, and the third by Karen Elkins. And they are looking at intracellular pathogens and trying to understand both the availability of vaccines that are currently on the market and how to improve them and to develop ways to monitor new vaccines that may improve on these.

And so I'll turn that over to Dr. Morris.

CHAIR KARRON: Thank you, Dr. Blake.

DR. MORRIS: Okay. Thanks for allowing me to participate in this meeting. Today I want to review the Laboratory of Mycobacterial Disease and Cellular Immunology, briefly review regulatory responsibilities and talk about our research accomplishments, at

least in the past four years and finally talk about activities within the public health community.

If you go to Slide 3, it illustrates the regulatory responsibilities and duties that we have. We have a whole spectrum of regulatory duties from providing preclinical guidance to reviewing IND submissions, reviewing BLAs, doing inspection, reviewing product labeling, product release documents, and also assisting in developing regulatory policy.

On Slide 4, summarizes the products that we regulate. We regulate vaccines, immunotherapeutics and diagnostics, probably most importantly in the past two or three years is regulation of INDs for new TB and malaria vaccines. Of course, these are two of the most important global vaccine initiatives currently.

Regulatory accomplishments are summarized for the past four years during the

site visit period. In the next slide, we've reviewed more than 700 IND submissions, participated in a number of pre-IND meetings, reviewed greater than 30 BLA supplements, reviewed a number of annual reports, coauthored guidance documents, made 18 presentations relevant to regulatory process, and actually co-organized the FDA/NIH workshop on regulation of TB vaccines.

So that's just a brief summary of our regulatory duties. And now, I want to go on to spend more time on the research.

Historically, we have been involved with four basic areas. First of all, looking at the molecular basis of disease pathogenesis, and for our lab that's largely TB and Francisella. Also looking at immune mechanisms associated with intracellular infections.

We have done a lot of work in the past 15 years on studying the effectiveness of novel TB vaccines. We have a standardized

aerosol challenge model in the lab for evaluating TB vaccines. And finally, more recently, we have become more involved in development of assays to characterize vaccine-related products.

As Milan mentioned, we have three research sections in our lab: molecular vaccine section, a micropathogenesis section, and an immune mechanism section.

The next slide, which I believe is Slide 8, lists the staff in my section. I have one staff fellow, two post-docs, and a technician. And it lists some of the collaborators we have. We collaborate with Bill Jacobs and Steve Porcelli at the Albert Einstein College of Medicine, with Bob Cedar at the Vaccine Center at NIH, with some folks at NCI, with investigators at the Aeras Global TB Foundation, and with public health -- or with Barry Kreisworth at the Public Health Research Institute in Newark.

Okay. Our section is focused on

three primary areas during the past four years. First of all, characterization of live attenuated TB strain; that has been a big effort in collaboration with Bill Jacobs and Steve Porcelli at Albert Einstein. We have also evaluated a number of novel TB DNA vaccines and spent a lot of effort in development of assays to facilitate vaccine -- TB vaccine development.

With support from NIH, we have been developing an in vitro potency assay for TB vaccines, which are -- which is sorely needed. And with support and collaboration from the Aeras Global TB Foundation, we have been developing a preclinical safety test for post-exposure TB vaccines. There is a concern in the TB community that administration of TB vaccines into people that were previously exposed to TB or infected with TB, I should say, will yield Koch-type reactions, so we're trying to develop a preclinical safety test which will address this concern.

We had a number of significant findings in the past four years. I've just sort of summarized four of them. First of all, demonstrated the effectiveness of a pro-apoptotic strategy for generating new attenuated TB vaccines, and this pro-apoptotic approach may be a new paradigm for developing TB vaccines, and that was recently published in Journal of Clinical Investigation.

We showed that BCG immunization protects against challenge by a number of different M.TB genotypes, and the reason this is important is because recent epidemiological studies and other preclinical studies have suggested that BCG may not be so effective because it doesn't protect against certain TB genotypes.

But we showed at least in mouse model that BCG is equally effective against a number of TB genotypes, and I think that has significant implications for future vaccine development testing.

As I mentioned, we have developed preclinical assays for assessing the safety and potency of post-exposure and prophylactic TB vaccines with support from NIH and the Aeras Global TB Foundation. And finally, and this is collaboration with Bob Cedar at the Vaccine Research Center, we showed that the frequency of multi-functional T-cells expressing Interferon-gamma, TNF-alpha, and IL2 correlate with level of vaccine-induced protection against TB.

So that suggests that these multi -- induction of these multi-functional T-cells may be a correlate of protective immunity against TB. And this was recently published in Nature Medicine.

The second section is headed by Mike Brennan, it's the mycopathogenesis section. Mike currently has a visiting fellow working for him, a post-doc, and an experienced technical person. He has a number of collaborators throughout the world,

including people at the Institut Pasteur, University of Maryland, Colorado State, University of Texas, and Catholic University of Rome.

They have focused in the past four years on two major projects, characterization of a heparin-binding hemagglutinin in cell-surface protein, a very interesting protein from TB. And I think in the last couple of years, they've focused largely on the characterization of novel multi-gene family of TB. There are nearly 100 of these PE/PE_PGRS genes encoded in the TB genome. The role of these genes is unclear in TB and so there is a considerable interest in labs throughout the world about defining what the role of these proteins are.

Some significant findings from Mike's lab section during the past four years are the following. First of all, they showed the differences in expression of certain PE_PGRS genes during infection may indicate

that they provide a novel mechanism of antigenic variation used by TB.

Nathalie Cadieux in Mike's group has shown that PE_PGRS proteins interact with mitochondria, which may lead to host cell injury and death and provide M.TB with a mechanism for escaping macrophages and other infected host cells. And also they have identified a PE antigen that elicits a strong TH1-like response and protects M.TB against challenge in an aerosol TB mouse model. And this MaPE antigen is being pursued as a new TB vaccine candidate.

Now, finally, Karen Elkins's group immune mechanism section. Karen currently has a visiting fellow, Siobhan Cowley, two post-docs, and two technicians. She has a number of collaborators, NIH; UNC Chapel Hill; University of Maryland at Baltimore; University of Victoria in British Columbia; University of Texas, San Antonio; University of New Mexico.

And Karen's group, in the next slide, which I think is Slide 17, has had three major focuses in the past four years. First of all, they provided a lot of reagents and information for tularemia vaccine research. I just want to emphasize this point. Post-9/11 there has been a considerable expansion of the Bio-Defense Program and an increased interest in tularemia research.

For many years, Karen has been a leading domestic tularemia researcher and with this -- when these new tularemia research programs were evolving in recent years, Karen has been an invaluable source of agents and information about Francisella host pathogen interactions.

Okay. So the second sort of interest or -- of this group in the past four years is understanding innate immune mechanisms, responses to intracellular bacteria, including Francisella tularensis and

M.tuberculosis and also in defining mechanisms by which B&T cells provide protection against intracellular bacteria, including Francisella and mycobacteria.

We have summarized a few of the accomplishments that Siobhan and Karen have had during the past four years, and they include -- they have looked at lot at this unique membrane TNF-alpha molecule and found out that it's a major mediator, a T-cell mediated control of Francisella and M.tuberculosis growth.

They also found that interferon gamma, although has a modest role in this whole process of controlling growth of these intracellular pathogens, probably is an unlikely reliable correlate, probably has only a modest role.

Secondly, Siobhan and Karen have identified this unique non-CD4/CD8 double negative T-cell subset, which appear to contribute substantially to adaptive immunity

against Francisella and mycobacteria at least in mice. And they have two nice general experimental medicine papers describing these cells.

And finally, Francisella species, they found that Francisella species contain a major pathogenicity island, which expresses about 25 virulence-related genes, and this could have an impact with respect to the evaluation of a safety of a live vaccine strain of tularemia.

So to summarize our research accomplishments, we had, during the past four years, 45 publications, including a number of publications in very prestigious journals, including Nature Medicine, TNAS, Journal of Experimental Medicine, Journal of Clinical Investigation.

We had 55 invited research presentations. We competed for external funding and actually got funded from 15 sources or 15 different projects. So that

summarizes the research.

I just want to briefly talk about our involvement with the public health community. We do a lot of work for the WHO. Mike has been involved with the GAVI Committee, TB Vaccine Initiative Advisory Board, Stop/TB Working Group. Karen has been involved with the tularemia network of the WHO.

We provide standard reagents for the WHO. We do some work with the CDC, especially in terms of skin test studies. We have been involved with the BTEP Program, all three of the PIs, the Biotechnology Exchange Program with Russian scientists. We do a lot of work with NIH, study sections, TB Vaccine Review Committee, Mike was on that. Karen has been on some NIH Blue Ribbon Panels.

I'm on the Advisory Committee for Elimination of TB. Mike and I have participated in the Federal TB Task Force. A number of us in the group do a lot of review

of scientific papers and are on editorial boards for scientific journals. And we have been involved with the organization of major scientific meetings.

Karen was a major organizer of the -- last year's international tularemia meeting, and Mike has been very involved with some of the TB vaccine meeting organizations.

And finally, we'll just talk about some outreach activities. We, as I mentioned, provide reagents and develop assays for tularemia and TB research in collaboration with the Aeras Global TB Foundation and the WHO. We actually developed and characterized TB challenge strains and a standard BCG vaccine for preclinical vaccine testing.

In labs throughout the world, we actually distribute these; we're asked by labs throughout the world to send us these strains so that we can have some sort of standardized preclinical testing of TB vaccines.

Mike and I have also been involved

with the development of standard tuberculins, and Mike's group has been involved in the distribution of anti-HBHA monoclonal antibodies and the production of HBHA knockout strains.

That's all I have to say about our lab. Thanks for your interest. Any questions?

CHAIR KARRON: Thank you, Dr. Morris. Any questions for Dr. Morris? Okay. Thanks again, Dr. Morris. I think, at this point, we'll move on. Christine, I think you have an announcement?

DR. WALSH: Thank you, Dr. Karron. As part of -- we will move on to the open public hearing section. As part of the FDA Advisory Committee meetings procedure, we are required to hold an open public hearing for those members of the public who are not on the agenda and would like to make a statement concerning matters pending before the Committee.

I have received one written comment. A copy of the statement has been given to the Committee Members. A copy has been placed in the viewing notebook at the registration desk and we will make -- and will be made part of the official meeting record.

Is there anyone in the room who would like to address the Committee at this time?

MS. GHOSH: I have a quick question. I'll identify myself.

DR. WALSH: Dr. Karron, we do have someone who would like to make a statement.

CHAIR KARRON: Okay.

DR. WALSH: Can you come up to the desk, so the Committee can hear you? And before that, Dr. Karron, would you, please, read the open public hearing general matters statement?

CHAIR KARRON: Yes. Both the Food and Drug Administration and the public believe in a transparent process for information

gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include the companies or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationship.

If you choose not to address this issue of financial relationship at the

beginning of your statement, it will not preclude you from speaking.

MS. GHOSH: Okay. My name is Jaya Ghosh. I'm from Cell Technology Incorporated. We sell elispot readers, and I just had a question about the TB diagnostic tests that are based on gamma interferon secretion assays. I wanted to ask Dr. Morris if he would like to make a comment on that. I heard about the TNF being more important protective correlates, so if you'll just, the implications of that work? Thank you.

DR. MORRIS: Good question. There are a number of -- I mean, there are a couple of diagnostics that are being developed, some of which have been licensed, largely based on interferon gamma. Our work would suggest preclinically that interferon gamma is not the only important cytokine in terms of controlling TB, but that has not been taken into the clinic as yet.

So it's going to take some clinical

studies to prove that. So far the FDA has approved some diagnostics largely based on interferon gamma release, so obviously we think that they do correlate with -- or they are effective.

DR. WALSH: Thank you, Dr. Morris.

CHAIR KARRON: Thank you. Is there anyone else who would like to make a presentation during this open public hearing?

DR. WALSH: Dr. Karron, I see no response.

CHAIR KARRON: Okay. At this time, I think we will take a five minute break to allow you to clear the room, and then we will reconvene in five minutes to begin the closed session.

DR. WALSH: Okay. If the Committee would stay on the line, if you need to take a break, that would be fine, but if you would just stay on the line with us, and we'll, as Dr. Karron says, reconvene in five minutes.

DR. HETHERINGTON: All right. This

is Seth Hetherington, and I will sign off at this point.

DR. WALSH: Thank you very much, Dr. Hetherington.

DR. HETHERINGTON: Thank you very much. I enjoyed it. Bye now.

DR. WALSH: Okay. Thank you.

(Whereupon, the open session meeting was concluded at 2:21 p.m.)