FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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CELLULAR, TISSUE, AND GENE THERAPIES
ADVISORY COMMITTEE

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TELECONFERENCE

November 20, 2006

The teleconference came to order at 2:15 in room 121 of Building 29, National Institutes of Health, Bethesda Campus. Dr. James Mule, Chairman, presiding.

PRESENT:

JAMES MULE, PHD	CHAIRMAN
DAVID HARLAN	CONSULTANT
MATTHEW J. ALLEN, DVM, PHD	MEMBER
MICHELE CALOS, PHD	MEMBER
JEFFREY S. CHAMBERLAIN, PHD	MEMBER
RICHARD J. CHAPPELL, PHD	MEMBER
STANTON L. GERSON, MD	MEMBER
FASHID GUILAK, PHD	MEMBER
LARRY W. KWAK, MD, PHD	MEMBER
SAVIO LAU-CHING WOO, PHD	MEMBER
DORIS A. TAYLOR, PHD	MEMBER
WALTER J. URBA, MD, PHD	MEMBER
KURT C. GUNTER, MD	INDUSTRY REP
GAIL DAPOLITO	EXEC SECRETARY
CATHRYN CARBONE, MD	CBER
WILLIAM FREAS, PHD	CBER
ROSANNA HARVEY	CBER
KATHLEEN CLOUSE, PHD	CDER
AMY ROSENBERG, MD	CDER
ELIZABETH SHORES,PHD	CDER
STEVEN KOZLOWSKI, MD	CDER
WAYNE RAY, PHD	CDER
BARBARA RELLAHAN, PHD	CDER
DANIELA VERTHELYI, MD, PHD	CDER
KEITH WEBBER, PHD	CDER

A-G-E-N-D-A

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

2:15 p.m.

CHAIR MULÉ: Let me just start by thanking everyone for their time in reviewing the summary statement that Dr. Harlan put together for the Site Visit Team. So, I appreciate your participation, and I know fully well how difficult it can be to be involved with this teleconference without first having a face-to-face, since some of the members of the committee are new, but I do appreciate that you were able to join us by teleconference.

MS. DAPOLITO: Thank you.

Okay, Doctor Mulè, I'll take the roll call now?

CHAIR MULÉ: Okay.

MS. DAPOLITO: Okay, if the members would just say here or present when I call your name, please, again.

Dr. Calos?

DR. CALOS: Here.

MS. DAPOLITO: Dr. Chamberlain?

Dr. Urba?

DR. URBA: Here.

MS. DAPOLITO: Dr. Gerson will join us late.

Dr. Tomford?

Dr. Allen?

DR. ALLEN: Here.

MS. DAPOLITO: Dr. Woo?

Dr. Guilak?

DR. GUILAK: Here.

MS. DAPOLITO: Dr. Kwak?

DR. KWAK: Here.

MS. DAPOLITO: Dr. Taylor?

DR. TAYLOR: Here.

MS. DAPOLITO: Dr. Mulè is here.

Dr. Harlan?

DR. HARLAN: Here.

MS. DAPOLITO: Dr. Gunter, are you on the line?

Dr. Chappell, are you on the line?

DR. CHAPPELL: Yes.

MS. DAPOLITO: Okay, terrific.

Okay, and I also at this time will read the conflict of interest statement.

"The Food and Drug Administration convenes today's meeting of the Cellular Tissue and Gene Therapies Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives all members

of the committee are special government employees or regular federal employees from other agencies and are subject to the Federal Conflict of Interest laws and regulations.

The following information on the status of this Advisory Committee's compliance with Federal Conflict of Interest laws, including but not limited to, 18 USC 208 and 21 USC 355(N)(4), 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, including but not limited to 18 USC Section 208, and 21 USC Section 355(N)(4). Under 18 USC 208, applicable to all government agencies, and 21 USC 355(N)(4), applicable to certain FDA committees. Today's agenda includes a review and discussion of intramural research programs in the laboratories of Immunology and Immunobiology, Office of Biotechnology Products, Center for Drug Evaluation and Research.

Based on the agenda, FDA determined that the committee discussion presents no actual or appearance of a conflict of interest for today's meeting. Dr. Kurt Gunter serves as the industry representative acting on behalf of all regulated

industry, and is employed by Hospra, Inc. Industry representatives are not special government employees and do not vote.

This conflict of interest statement is available for review at the handout table on site. We would like to remind the members, 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."

Also, I would like to ask the committee if you can mute your phones except when you are talking, but right now we don't hear too much background noise, so that's pretty good. And, I wanted to tell the committee, the proceedings today are all being transcribed on the open portion of the meeting, those transcripts will be posted on the FDA website after the meeting.

And, Dr. Mulè, should we go around the room here and introduce the FDA folks?

CHAIR MULÉ: That would be great.

MS. DAPOLITO: Okay.

Keith, Dr. Webber, shall we start with you? I know you are on the phone.

DR. WEBBER: Yes, Keith Webber, I'm Deputy Director of the Office of Pharmaceutical Science here in the Center for Drug Evaluation Research.

DR. WOO: Hello, this is Salvio Woo from-- joining.

MS. DAPOLITO: Thank you, Dr. Woo.

DR. WOO: Okay, thank you.

DR. CARBONE: This is Dr. Carbone from CBER.

DR. CLOUSE: Kathleen Clouse, CDER.

DR. WEINBERG: Wendy Weinberg, CDER.

DR. RELLAHAN: Barbara Rellahan, CDER.

DR. KOZLOWSKI: Steve Kozlowski, CDER.

DR. VERTHEYLI: Daniela Vertheyli, CDER.

DR. ROSENBERG: Amy Rosenberg, CDER.

DR. SHORES: Elizabeth Shores, CDER.

MS. DAPOLITO: Okay, and Dr. Mulè, there are no members of the public in the office, in the room here. Also, Rosanna Harvey is with us.

DR. RAY: Wayne Ray, CBER.

MS. DAPOLITO: And so, it's all FDA in the

room, we are -- we do have a video company here and a transcriber, so that's who is on site at the moment. *(2:20:55 JS)*

CHAIR MULÉ: Okay.

MS. DAPOLITO: Can I ask if there are -- Dr. Gerson, or Gunter or Tomford joined us? Okay.

So, Dr. Mulè, I'll turn it over to you.

CHAIR MULÉ: Okay. So, Gail, has there been any feedback on the open public hearing?

MS. DAPOLITO: No, there's been no requests, and it doesn't look like there's anyone in the room that would request time.

CHAIR MULÉ: Okay, great.

So, to the committee, you probably received from Gail, I believe it was on Friday, the slide sets for an update by several presenters from the Division of Therapeutic Proteins in Division of Monoclonal Antibodies that are pertinent to the summary statement of the Site Visit Team that was set up by Dr. Harlan.

So, I guess what we can do is go through the slides, if you have them loaded on your computer, as the presenters take us through them. And then, at the end of that period of time, we'll enter into the closed session, where we'll discuss, we'll have

presentations by Dr. Carbone, and also the presentation of the Site Visit Report from Dr. Harlan.

We'll then have some discussion, and then we'll vote, and the vote will be on the question, does the committee accept the report of the Site Visit Team?

DR. CHAPPELL: This is Rick Chappell. I wanted to say apologetically that I teach class at 3:30 Eastern Time, so I'm going to have to bow out then.

CHAIR MULÉ: Okay. Okay, Gail, so I guess we can go ahead with the introduction from Dr. Rosenberg.

MS. DAPOLITO: Okay. Actually, Dr. Webber, from the FDA Office of Pharmaceutical Sciences, will give us just a brief introduction before Dr. Rosenberg.

CHAIR MULÉ: Okay, great.

DR. WEBBER: Yes, this is Keith, and I just wanted to give a little bit of brief background and introduction be fore the presentation starts, just to orient everyone, I know there are some new folks on the committee as well.

With regard to OPS, this office, OPS, and we oversee four other offices within CDER that are

responsible for the laboratory research and the review of product manufacturing. These offices include the Office of Biotechnology Products, which is the home office of the researchers that are being reviewed today.

The Office of Biotechnology Products was formed in CDER when the two divisions, DMA, Division of Monoclonal Antibodies, and Division of Therapeutic Proteins, got transferred over from the Center for Biologics to the Center for Drugs, back in 2003. So, that sort of gives a little bit of perspective about the relationship between CDER and CBER with these researchers.

And, the folks under review today are going to be Dr. Kozlowski, who is the Director of the Office of Biotechnology Products, as well as a researcher in DMA, Division of Monoclonal Antibodies. He's being reviewed to assess his research progress, ----------.

Dr. Vertheyli and Dr. Weinberg are being considered for a ----------, and Dr. Rellahan, in the Division of Monoclonal Antibodies, is being considered ----------.

DR. CARBONE: Keith?

DR. WEBBER: Yes.

DR. CARBONE: Excuse me, this is open session, this is Kathleen Carbone, personnel actions are confidential, so --

DR. WEBBER: Okay, these aren't actions that are actually underway, but they are things for consideration.

DR. CARBONE: This is confidential stuff, so what we need to do is do the science first, and then when we close the session we'll do that review. We'll do the science and organization presentations.

DR. WEBBER: Okay.

DR. CARBONE: Okay, sorry.

DR. WEBBER: In closing, I'd like to certainly thank Dr. Harlan and the Site Visit Committee, as well as the CTGT Advisory Committee for taking time from their busy schedules to participate in this evaluation.

Again, the site visit system is really extremely valuable to us, as a component of our quality assurance system here at the FDA, and, particularly, I'd like to thank the Site Visit Team for documenting within their report such strong report for the researcher reviewer model, which is critical to ensuring scientifically informative relevant reviews of products at the FDA.

And, with that, I thank you.

CHAIR MULÉ: Thanks, Dr. Webber.

Let's move on to Dr. Amy Rosenberg.

DR. ROSENBERG: Yes. I just have a few comments. I'm Dr. Vertheyli's Division Director, and I just want to talk very briefly about the division, the laboratory she's in, and her contributions.

Next slide, please.

So, this is the structure of our division. Dr. Vertheyli is located in the Laboratory of Immunology. The Laboratory of Immunology is directed by Dr. Elizabeth Shores. The people who are highlighted in red are people we have lost. Particularly difficult is the loss of full-time reviewers, which puts added stress on our research reviewers and all other reviewers, in terms of the amount of time that they have for addressing the research programs.

Next slide.

I have an update of this slide. This is a little bit old. We now have, currently, 65 total licensed products with 47 novel molecular entities within our division. We have a mix of proteins derived from natural sources and recombinant sources, mostly recombinants. We also have engineered versions

of prototype products that are designed, engineered to enhance critical product quality characteristics, such as pegylation, hyperglycosylation, mutations to enhance specificity of activity. We deal with products produced in a multiplicity of cell substrates, including bacteria, yeast, human cells, transgenic animals and transgenic plants. And, the manufacturing process is unique for each of our products.

Next slide.

The Laboratory of Immunology is the primary reviewers for the products you see one through nine that are bolded, including the interons, the interleukins, chemokines, toxins, including botulinum toxin products, the most toxic products known to man, toxin fusion molecules, immunomodulators, innate immune system components, bacterial adjuvants, and I want to point out that Dr. Vertheyli's expertise is particularly crucial in these three areas of immunomodulators, innate immune system components and modifiers, as well as adjuvants.

However, the Laboratory of Immunology also serves as critical product reviewers for all of our therapeutic protein products, in reviewing the immunogenicity of their products. As you all know, all

proteins are subject to generation of immune responses, and this can be particularly problematic with some of our products whose endogenous counterparts subserve unique biological functions such as Epo, GCSF, et cetera.

Next slide, please.

So, let's get to Dr. Vertheyli's contribution to our division and laboratory. So, Dr. Vertheyli functions at the highest levels in both the research and regulatory arenas. As you know, she's a nationally and internationally recognized expert in immunology, and she's a leader in the field of the innate immune system. Her research program provides the agency with critical expertise in the evolving and highly-active area of innate immune system modifiers. And so, her expertise really allows for the highest caliber evaluation of these developing products that impact both the innate and, consequently, the adaptive immune systems.

Her research program also provides the agency with the expertise essential to evaluate the quality of the immune assays used to assess the immunogenicity of therapeutic protein products, which is rather critical.

As well, her regulatory activities are of

the highest caliber and involve all levels of regulatory actions. She's contributed to policy formation, and she's been a co-author on a guidance document as well as a critical contributor to another guidance document on immunogenicity.

She serves as the CDER representative to a government-wide working group called ICCVAM that evaluates assays critical to product regulation. She has been our representative to national and international meetings, speaking on regulatory issues. She provides, again, expert regulation of products that are components of or act on the innate immune system. She, as well, provides expert regulation of botulinum toxin products, which are very challenging, and she also has served as consultant to other agency centers on immunogenicity issues.

Next slide.

Last slide is, we are in full agreement with the site visit assessment that was communicated to us by the committee immediately following the site visit, to convert Dr. Vertheyli to Senior Investigator at the GS-14 level, and that's all I need to say.

CHAIR MULÉ: Thanks, Dr. Rosenberg.

Are there questions from the committee for Dr. Rosenberg?

Okay.

DR. TAYLOR: This is Dr. Taylor, I actually have a question.

How much of Dr. Vertheyli's time is spent in regulatory work versus research? Do you have any sense?

DR. ROSENBERG: Yes. I would say that up until, you know, and we can't protect her time. As you saw, we are losing full-time reviewers. Full-time reviewers are incredibly important, because they can take up a lot of the work otherwise assigned to our research reviewers. It's very difficult to protect the research time for our research reviewers, but as you know, it's critical because otherwise we lose the critical expertise and it becomes just a slow-boiling negative effect.

So, it's very critical for us to have sufficient personnel to handle all of the regulatory work.

CHAIR MULÉ: Okay. Other questions?

Okay, thanks.

DR. CARBONE: Dr. Mulè?

CHAIR MULÉ: Yes.

DR. CARBONE: This is Cathy Carbone. I wanted to sort of clarify that, of course, we are

expecting the committee to give us their assessment on Dr. Vertheyli's research quality, et cetera. So, I appreciate Dr. Rosenberg's slanting her thoughts, and I appreciate the very important regulatory comments, but, of course, we are interested in the committee's thoughts on Dr. Vertheyli's regulatory quality. I just wanted to clarify.

CHAIR MULÉ: Okay, great, thanks.

Okay, let's move on to Dr. Vertheyli.

MS. DAPOLITO: Dr. Mulè, can I just ask, did Dr. Gerson join us? Not yet? Okay.

DR. GERSON: He did. I'm here.

MS. DAPOLITO: Oh, okay, thanks.

DR. VERTHEYLI: Good afternoon, and thank you to the committee for taking the time to do this. My name is Daniela Vertheyli, and I joined DTP in 2002 and established a lab that has myself and three other people --

MS. DAPOLITO: Could you speak up, please?

DR. VERTHEYLI: I'll move closer to the microphone. Is that better?

CHAIR MULÉ: That's better.

MS. DAPOLITO: Yes.

DR. VERTHEYLI: So, I was saying, I head a small lab with two staff fellows, Montserrat Puig and

Joao Pedras a technician, the focus of the program is in the identification and characterization of innate immune response modulators.

We are, basically, interested in assessing the safety and effectiveness of immune regulators, vaccine adjuvants and immunoprotective agents in infectious diseases. In particular, -- bioterrorism agents and emerging pathogens.

To that effect, we work in the development of murine and primate models to assess safety and efficacy. We assess the impact of age, gender and immune competency, again, on the same type of products. And, over the last year we incorporated a new program that looks at the impact of impurities that trigger the innate immune system on product immunogenicity.

So, I'm just going to highlight some of the findings that we've had over the past four years. We have demonstrated that systemic administration of CpG ODN, which are a total of nine agonists that directly stimulates the innate immune response, protects neonatal mice from (?? 2:34 p.m.) meningoencephalitis due to Tacaribe arenavirus, which is a model for Class A arenaviruses, which are agents of hemorrhagic fevers. We've developed and

characterized the first primate model of immunoprotection demonstrating that administration of CpG ODN alone significant reduces the severity of continuous leishmaniasis. This protection is systemic, can be attained after the lesions are established, and does not interfere with subsequent life-long immunity.

We have also showed that CpG ODN accelerate and improve the protective effects of vaccines to Hepatitis B virus in healthy as well as in immunocomprised SIV infected macaques, and I should like to add that those findings were used as parts of the base for an IND that came into the agency looking at the addition of these type of compounds to an (??2:35 p.m.) vaccine for immunocompromised subjects.

We also have developed a novel (??2:35 p.m.) form of CpG ODN that results in manufacturing issue of product aggregation in sequences containing poly-G strands. This approach can also be used to prolong the immunoprotective effect of therapeutic ODN, and this has applications both in the field of bioterrorism, and that one of the shortcomings of potential use of immunomodulators as first response agents was the narrow therapeutic windows that they have, and we found a way of prolonging that. And

also, it may have a positive impact or increase the effectiveness of these drugs in cancer treatment.

In terms of what progress we've made since the site visit, in the project assessing the contribution of low levels of impurities that can trigger cold-like receptors to increase the immunogenicity of therapeutic vaccines, we'd one studies both in vitro and in vivo. In vitro we've shown that sub-optimal concentrations of different TLR ligands synergize to stimulate B cells and (?? 2:37 p.m.) cell activation, and we've seen in vivo that this reflects, or this causes an induction of an accelerated IgG antibody response. We found this in a model of ovalbumin, where we've seen that simultaneous addition of sub-optimal levels or sub-stimulatory levels of different TLR ligands can increase the immunogenicity up to two logs, so, in essence, you would have a two logs lower LPS with use of significant levels of antibodies in the presence of an additional TLR ligand.

We have an additional ongoing study looking at whether these sub-optimal levels of TLR ligands have an effect on T cell tolerance.

In terms of the use of innate immune response modifiers, in a mouse model of viral

meningoencephalitis by arenavirus. Over the past five months, we assessed the contribution of selected immune cell type cytokines and chemokines and determined what their role is in pathogenesis. We established that antibodies to TNF alpha induced 100 percent survival in these animals, but result in chronic infection, and have demonstrated that the co-treatment of mice with anti-TNF antibodies plus CpG ODN result both in 100 percent survival plus a reduction in viral load.

Importantly, the increased protection is evident even in immunocompromised mice, such as the iNOS KO mice, that could not be rescued by any of the conventional therapies.

In ongoing studies, we are starting to look at the effects of TLR organisms in the developing central nervous systems in the absence of infection. We think this is important in terms of safety of these compounds.

So, as far as updating the output of the lab as it stands in the site visit report, since June, 2006 we had -- at that time we had reported we had a chapter in press, that chapter has now been published. Also, we had submitted a manuscript in conjunction with Bonnie Dittel's group, that one is now in press.

In addition, we have now submitted and got an acceptance for a manuscript of which I'm particularly -- I think it illustrates very nicely the capabilities of the lab. There's a manuscript that looks all the way from the synthesis and design of an immunomodulatory molecule. It looks at it's immunostimulatory activities in vitro and in vivo, and then the immunoprotective activities in vivo in primates. So, it, basically, spans the whole expertise of the lab, and that is now in press with Nucleic Acid Research.

We've also submitted and got acceptance for a chapter in a book on therapeutic oglionucleotides, and we've submitted an additional manuscript on BAFF and B cells.

In terms of additional accomplishments, we've also submitted a patent for our discoveries in terms of the treatment of mice with antibodies to TNF alpha alone or in combination with CpG ODN. I've presented data at an invited seminar at Boston University. My lab has presented data at the 2nd Annual Meeting on Oglionucleotide Therapeutic Society, and I'm happy to say that Montserrat Puig, who also presented data, got one of three awards for best data that were presented.

The other posted in the lab where Pedras presented data on the anti-TNF antibody use in meningoencephalitis at a FASEB Conference on immune interactions, and then the NIH-wide immunology retreat, and has been awarded what's called the FARE award, which is a prestigious award for post-doc fellows.

Now, Amy Rosenberg has mentioned, it is often the question of why do we need somebody who actually knows about innate immunity in the Division of Therapeutic Proteins, and I'd like to point out that the innate immune system not only is composed of dentritic cells, monocytes, B cells and other immune cells, but it, basically, entails a number of processes that are independent processes that include phagocytosis, antimicrobial proteins, compliment interferon-inducing responses in antimicrobial peptides. Innate immune regulators affect all of these processes, and we have over the past four years received submissions that target all of the ones that are circles in red in your slides.

Lastly, I'd like to sort of summarize the regulatory work that has been done over the past five months. We've contributed to one new BLA, actually, two new BLAs, in terms of immunogenicity, which dealt

with a couple of CMC supplements with BLA. One new pre-IND, and one new IND, several annual reports and supplements, and lastly I'd like to say that I've been asked to be a session chair for the Infectious Disease Section on an upcoming FDA and DIA meeting on therapeutic oligonucleotides.

\ And, with that, I'll answer any questions.

CHAIR MULÉ: Thanks, Dr. Vertheyli.

Questions from the committee?

All right, well, thanks for the update. I think we can move ahead.

DR. GUNTER: Jim, this is Kurt Gunter. I apologize, I had to dial in late, I had a minor emergency, but I apologize, I'm here now.

CHAIR MULÉ: Okay, great, Kurt.

Okay, let's move on to Dr. Kathleen Clouse.

DR. CLOUSE: Okay. I would like to mention, I am the Acting Director for the Division of Monoclonal Antibodies. the Division of Monoclonal Antibodies is structured a bit differently from the Division of Therapeutic Proteins, but the flow chart for that is in the site visit book and so on.

We, basically, have one regulatory review branch composed of eight full-time reviewers, and then

we have three research-based laboratories where the principal investigators do research and regulatory review work.

The Division of Monoclonal Antibodies handles, not just monoclonal antibodies, but bi-specific antibodies, combinations of antibodies that range anywhere from combinations of two to more recently 25 monoclonal antibodies. We also do epsi fusion proteins that can function as agonists or antagonists, antibody toxin conjugates, antibody radionuclide conjugates, and so on.

The mission of the DMA is shown in the next slide, is to ensure that safe, and efficacious, and high-quality monoclonal antibody and related products are available to the American people to diagnose, prevent and treat the illnesses that afflict them. And, more importantly, or most importantly, to maintain and retain a diverse, knowledgeable, and scientifically based and dedicated staff.

Now, it's been published recently that monoclonal antibodies now comprise the majority of recombinant proteins currently in the clinic, with more than 150 products and studies sponsored by companies located worldwide. Now, their targets, clinical indications, mechanisms of action, and

potential adverse events, are diverse and complex, which necessitates a knowledgeable and scientific staff.

So, I'd like to just go through very briefly, because we do have three principal investigators who were site visited, and give you a brief background on each, and let them expand on their own programs in greater detail.

First, I'd like to introduce Dr. Wendy Weinberg and talk about Dr. Weinberg. She was selected for a tenure-track staff fellow position in 2000, following a national recruitment effort for an expert in oncology. She has established an oncology -- an independent oncology research program, with an emphasis on squamous cell carcinogenesis, in part to identify potential biomarkers and molecular targets, and also to facilitate the development and review of pre-clinical models that are needed.

Dr. Weinberg had to assume an unusually heavy regulatory workload early in her appointment at FDA, due to the loss of personnel with oncology expertise, and she has maintained that throughout her tenure-track appointment.

The next slide, Dr. Weinberg reviews numerous products for oncology and dermatology, both

at the IND and BLA level. She has performed intra and inter-center regulatory consults. She's participated in pre-approval inspections for monoclonal antibody products. She's a member of the CDER Committee for Advanced Scientific Education, and she's served as a Co-Director for a CASE workshop about the FDA review of biologic products from A to Z, that was actually used for training of clinical reviewers in the Center for Drug Evaluation and Research, subsequent to our transfer from the Center for Biologics.

She served as a session co-chair at the AACR annual meeting, and was on the program committee. She was an invited speaker and also a session co-chair for the International Skin Carcinogenesis Conference. She served as an adhoc reviewer for numerous scientific journals, some of which include Cancer Research, Oncogene, Molecular Cell Biology, and she has also served in the review of grants for international funding agencies.

She recently was appointed Associate Editor for the Journal of Molecular Carcinogenesis.

The second individual who was under review for site visit is Dr. Barbara Rellahan. Dr. Rellahan, actually, has served as a researcher reviewer at FDA since 1996, first as a staff fellow and then upon her

conversion to a staff scientist position, she served as a reviewer and researcher as a staff scientist.

She was selected for tenure-track independent staff fellow position in 2004, after an HHS-wide recruitment, to replace a principal investigator who left the division. She has since established an independent research program to study signaling cascades that serve as targets of immunomodulatory antibodies, in order to understand how their modulation will affect lymphocyte function.

She's made significant progress as an independent investigator, despite maintaining her heavy regulatory workload that she's accumulated since 1996.

Her critical knowledge and expertise have been vital to the FDA regulatory mission, that's been shown most eloquently recently by her critical role in the FDA response to issues raised by the United Kingdom's incident with the anti-CD28 monoclonal antibody TGN1412, and this was the subject of a lot of discussion at the site visit during her presentation, and I understand in the closed sessions as well.

Dr. Rellahan reviews numerous products for autoimmune diseases, Graft Versus Host disease, transplantation and cancer, again, both at the IND and

BLA level. She also has sent inter and intra-center regulatory consults, participated in pre-approval and biennial inspections as a product expert.

She's served on regulatory working groups for guidance document development, and again, as mentioned before, she was the FDA's representative to the U.K.'s expert group to review adverse incidents during clinical trials of TGN1412.

She was an invited speaker in 2001 and 2004 to the International Immunology Congress. She's been a DMA member on the Committee for the Advancement of CBER Science, an adhoc member of the CBER/CDER Promotion and Conversion Evaluation Committee, and also an adhoc reviewer for scientific journals, including The Journal if Immunology, Molecular Cell Biology, and The Journal of Biological Chemistry.

The last person who was up for site visit in the lab of Immunobiololgy is Dr. Steven Kozlowski. Steve joined the FDA after a national recruitment in 1993. He established an independent research program that was focused on cell/cell interactions, looking, specifically, at T cell activation and migration in order to investigate the influence of biologic therapeutics.

He acquired and maintained a heavy

regulatory workload since he served as both a clinical and a product reviewer while in the Division of Monoclonal Antibodies, for antibodies that target cell/cell interactions and act on adhesion and co-stimulatory molecules.

Dr. Kozlowski has participated in pre-approval and biennial inspections as well. He has served on regulatory working groups for guidance and document development. He also served as an instructor for the Team Biologics inspectors and the ICH training courses. He's been a member of the CDER Committee for Advanced Scientific Education, an adhoc reviewer for scientific journals.

He served as Chief of the Laboratory of Immunobiology from 2003 until shortly after the site visit, and due to his heavy administrative responsibilities we currently have an acting lab chief.

He served as Acting Deputy Director, and then Acting Director, for the Division of Monoclonal Antibodies from 2003 to 2005. In 2005, he assumed a position as Acting Director for the office of Biotechnology Products and was appointed the Director as of May, 2006.

He has acquired numerous additional

administrative responsibilities as OBP transitioned administratively from CBER to CDER, and those encompassed quite a bit of his time the past three years.

So, I'd like to leave you with one thought, we feel it's impressive that in spite of the increasing regulatory workload and diminishing resources, these individuals have continued to perform quality research which supports the mission of OBP and the agency.

Thank you.

CHAIR MULÉ: Okay, thanks, Dr. Clouse.

Questions?

DR. TAYLOR: I have one question, regarding Dr. Kozlowski, this is Doris Taylor. You said he is no longer serving as the Chief of Laboratory of Immunobiology, and he's no longer the Deputy Director and Acting Director for DMA, is that correct?

DR. CLOUSE: That's correct. He served as Acting Deputy Director when Dr. Webber was the Director of DMA. When Dr. Webber moved up to the Office of Biotechnology Products, Dr. Kozlowski then became the Acting Director for DMA, and then when Dr. Kozlowski became the Acting Office Director he then

gave up the Acting Division Director position, which I now hold.

DR. TAYLOR: Okay.

CHAIR MULÉ: Okay, great.

Let's move ahead. Dr. Weinberg.

DR. WEINBERG: Okay, thank you.

The overall goal of my lab is to delineate the molecular mechanisms that contribute to squamous carcinogenesis, and this is for the purposes of defining critical pathways and identifying potential biomarkers and molecular targets, but also to aid in optimization of bioassays, which are a critical parameter for characterizing protein products, and to aid in the development and review of relevant pre-clinical models that can be used for screening potential targeted therapies.

I've outlined our regulatory responsibilities of my laboratory on the next slide. Approximately, 40 percent of the submissions to the Division of Monoclonal Antibodies are targeted to cancer indications. And, as part of this division, my lab reviews monoclonal antibodies or antibody-related fusion proteins, primarily, designed for the diagnosis or treatment of solid malignancies. And, these can be agonist antibodies, for example, to death receptors,

or they might be molecules designed to block growth stimulatory signals. We also have immunoconjugates to target toxins to malignant cells, as well as a variety of radiolabled antibodies that are designed for diagnostic and therapeutic use.

The pathways that are targeted by these products may also be applicable for other disease indications, so I also work with products within other disciplines in CDER, and I didn't mention fusion proteins, but we have several of those as well.

So, I have been handling -- I have, approximately, 25 new molecular entities that I've dealt with as INDs, and I also deal with licensed products. I was on the BLA Committee for Herbitox, and I am responsible for all CMC post-licensing supplements for Herceptin.

In addition to my own regulatory work, I oversee the regulatory reviews of a staff fellow in my lab, as well as an NCI post-doctoral fellow who is in our lab through the Interagency Oncology Task Force Agreement between NCI and FDA.

On the next slide I've highlighted some of my scientific accomplishments since joining FDA as a tenure-track investigator. Dr. Clouse has mentioned some of these. They include publications in peer

review journals, and I currently have two manuscripts in preparation, in addition to what's on my CV. Also, invited speaking engagements and acting as co-chair or on the program committee of national and international conferences, as well as editorial work for journals, both as a reviewer and as an Editorial Board member for molecular carcinogenesis.

In terms of my research, I'll refer you to the next slide. My lab is focused on p63, which was originally identified as a family member of the tumor suppressor protein p53. Loss of p53 is believed to contribute to cancers in many organ sites, and p63 is essential for squamous development, and the gene has been found to be amplified in squamous cell cancers of several organ sites, most notably skin, lung and head and neck, and you are aware that cancers of the lung and head and neck have very poor prognosis and do not respond well, patients do not respond well to standard therapies.

The p63 gene is expressed as multiple isoforms. One of these isoforms, which is referred to as the delta N form, lacks a p53-like transactivation domain, and so can block p53 function, and this may be part of what over-expression of this gene product might be doing in cancers, but it's still not clear.

So, the role of p63 over-expression cancer development, as well as its contribution to the response of a patient to treatments, is not clear.

So, we've defined two specific aims, which I've shown on the next slide, to define the biological impact of p63 gene over-expression on epithelial -- normal epithelial homeostasis and on squamous carcinogenesis. And, we use the mouse epidermis as a model system for studying squamous epithelium. Among the goals are to understand the mechanism of action of p63 protein products, and to identify interacting signaling pathways that might offer potential targets of directed therapies. And, we have a second aim, to develop new models that will allow us to dissect the roles of these pathways in multi-step cancer pathogenesis, as well as the cellular response to cancer therapies.

On the next slide I have a summary of some of our findings. We've determined that p63 isoforms are expressed in keratinocytes under normal conditions, and that they are differentially regulated during keratinocyte differentiation.

A delta N isoform, which is (delta)Np63(alpha), is a marker of keratinocyte proliferation, and it's up-regulated in

experimentally-induced squamous cancers, similar to the up-regulation that's observed in human squamous cell cancers.

\ So, to mimic this over-expression we've developed adinoviruses to test the effect of over-expressing, the contribution of over-expressing p63 in the cell type, and we found that while they can block p63 it also has a p53 independent activity in regulating gene transcription that's cell-type specific. And, notably, that keratinocytes over-expressing (delta)Np63(alpha) display defects in growth regulation and differentiation specific gene expression that is consistent with the over-expression observed in human cancers.

To understand the mechanism by which p63 affects cell growth and differentiation, we used a transcription factor profiling system, and as you can see on the next slide we found that keratinocytes over-expressing (delta)Np63(alpha) have increased nuclear levels of the NF(kappa)B sub-unit c-Rel, and this corresponds to increased phosphorylation of the c-Rel protein, as well as increased transactivation by NF(kappa)B.

And, using SINRA we've established that this is data since the site visit we've established,

that this transcriptional activity is due to c-Rel.

Also, using a super repressor of NF(kappa)B we were able to determine that NF(kappa)B activity is required for the proliferative response observed in the loss of regulation of growth observed in keratinocytes over-expressing (delta)Np63(alpha).

So, we wanted to extend these studies to human cancers, and set up a collaboration with Carter Van Waise. I showed some of these data at the site visit. Dr. Van Waise has a clinical group, clinical program on campus, and so along with him we have established that p63 expression in normal human mucosa is associated with nuclear c-Rel, and that both p63 and nuclear c-Rel are up-regulated in samples of human head and neck squamous cell cancers.

We have some biochemical data that we've gotten since the site visit, that demonstrate that p63 and c-Rel associate both in mouse keratinocytes and also this is held up in human head and neck squamous cell cancer cell lines.

We are currently writing this up for publication, and in our future studies we intend to study how the molecules associate and what is down stream of NF(kappa)B in this setting.

We also, as I mentioned, have a second

aim, which is to develop models to dissect the contribution of p63 to cancer development and therapeutic response, and on the next slide I've outlined a scheme that we are using, it's an inducible transgenic model that we've developed to manipulate the expression of (delta)Np63(alpha). We are doing this work in collaboration with Adam Glock at Penn State University, and we've identified two lines of transgenic mice that express inducibly (delta)Np63(alpha). We are currently characterizing the phenotype, and we are bringing up one of these lines for chemical carcinogenesis protocol to determine the stage of cancer development at which (delta)Np63(alpha) might act.

We also intend to use these mice to further explore the contribution of c-Rel within this model system, and also to apply it to test treatment strategies.

So, that's where things stand right now.

CHAIR MULÉ: Great, thanks, Dr. Weinberg.

Questions?

Okay, terrific. All right, we are right on schedule. Let's move ahead to Dr. Rellahan.

DR. RELLAHAN: So, I am going to talk about my program looking at the regulation of

PLC(gamma)1 in lymphocytes. I have two full-time technicians, Karen DeBell and Laurie Graham, who work in the lab. Laurie Graham also does review work as well as research.

If you go on to the second slide, our lab is primarily responsible for the review of regulatory submissions that look at clinical use of antibodies or antibody-related molecules for the treatment or prevention of autoimmune diseases, Graft Versus Host disease, transplant rejection and anti-cancer therapies.

Probably about half the antibodies we look at are aimed at T cell surface markers. We have a number against the CD3 complex, as well as a number against post-stimulatory or inhibitory receptors.

We actually have a number of antibodies that are directed against cytokine receptors, as well as natural killer cell receptors.

On the next page, I just listed a select few of the regulatory responsibilities. I do supervise the work, regulatory work, of any staff fellow or staff scientist in the lab. Our lab is responsible currently for the review of 34 unique molecular entities, and I am responsible for BLA supplements and the biennial inspections for Zenapax,

which is an anti-L2 receptor antibody on OKT3. In the past year or so, I also acted as a consult reviewer for FC region-related issues for the Abatacept BLA.

I'm currently the co-chair of the DMA committee to rewrite the monoclonal antibody points to consider guidance document, and I'm serving as the FDA representative to the U.K.'s expert scientific group on the DGN1412 issue.

On the next slide, I just listed some of the regulatory presentations since my last site visit. Toward the bottom, I just want to point out in June I presented -- I had two presentations at the AAPS National Biotech Conference. I went to London two times during the spring and summer for the U.K. Scientific Expert -- Expert Scientific Group, and in another week or so I'm going to participate and present at the CDER Science Rounds, which is going to discuss the issue of TGN1412.

On the next slide, I'm turning now to the research program. We look at PLC(gamma)1 as a marker of lymphocyte activation, and the goal of the laboratory is to use our understanding of the regulation of PLC activation on lymphocytes, and then apply this knowledge to help in our regulation of immunomodulatory therapeutic antibodies, and maybe to

understand and help predict adverse drug events.

The next slide just lists the three specific aims of the laboratory as outlined in my site visit package. And, if you go to the next slide, during the site visit I did present data from studies where we were looking at the role of the SH2C domain in PLC activation, and I show data in which we have found that the carboxy terminal SH2 domain in combination with the immunoterminal split plextron domain, TPLC in a closed and inactive configuration in unstimulated cells, and then after receptor stimulation the immunoterminal FH2 domain of PLC interacts with phosphotyrosine residues, and this induces a confirmational change in PLC that helps it open up and become catalytically active. And,. we've had this work accepted for publication in Molecular and Cellular Biology.

On the next slide, these are sort of the future aims of this project. We were looking at why raft-targeted PLC construct demonstrates deficient activity in T lymphocytes, and I want to point out that we used raft-targeted PLC, it was actually proved to be very helpful in our studies looking at the SH2C domain, and recently we have found that the raft-targeted PLC has a marked increase in the level of

serine phosphorylation compared to wild type PLC.

Serine phosphorylation in EGF receptor stimulation has been associated with decreased PLC activity, PLC has decreased activity, so we are planning now on investigating the role of serine phosphorylation of PLC during lymphocyte activation.

During my site visit and sessions I had with members, there was a certain amount of discussion that it would be very nice if we could get more structural data on the types of changes that we think are going on with PLC, and so I've been speaking with Dr. Daron Freedberg, who is in the Office of Vaccines at CBER, he runs their NMR lab and is an expert on glycoprotein structure, and he was very -- very interested in working with us, looking at PLC confirmation. He suggested that we first begin doing circular dichroism analysis on different GST fusion proteins we have in lab to see if whether when the SH2 domains bind to tyrosine phosphorylated residues there is a confirmational change, and then we'll move on to NMR.

If you go on to the next slide, this is about specific aim number two, where we are looking at the role of tyrosine phosphorylation in PLC activation. Specifically, right now we are trying to

characterize the interaction between the SH2 domains of PLC and the phosphotyrosine residues within PLC. We are trying to determine whether this interaction mediates (??homodyma 3:09) formation or whether it mediates an intracellular, intramolecular association.

We've been looking more at the specificity of this interaction, looking at the ability of the SH2 domain -- the immunoterminal SH2 domain to bind to specific peptides, phosphorylated peptides. During the site visit, Dr. (??Peer 3:09) suggested we vary the distance between the tyrosines that we've made peptides, where there is differences in the spacing.

So, go on to the next slide. I just wanted to mention the critical path initiative project in the lab, in the site visit package we had outlined that we would -- the aim there was to try to characterize and validate phospho flow to see if it could be used to characterize antibodies and be used as a potency assay, but after the incident in the U.K., where there were healthy volunteers given the CD28 antibody and they had acute life-threatening cytokine release, this project has sort of undergone a little bit of a variation, and right now what we are trying to do is to -- we think that it would be very nice for us to have a panel of assays that we could

ask sponsors to do if we had concerns about an antibody, so that we could sort of characterize agents as to their potential to induce cytokine release.

And, it might seem somewhat obvious that you look at cytokine release, but the anti-CD28 antibody actually didn't induce cytokine release in vitro, and only induced a small amount of cytokine release in animal models. And so, it's clear that we need some other assays, and so we've geared this part of the projects to look at other -- evaluate the use of other assays.

And then on my last slide, as part of this we've contracted with ProMap Biotechnologies to generate an antibody to the CD region of CD28, and we'll screen these antibodies to identify any that can induce proliferation of T cells, and, therefore, would mimic the activity of TGN1412, and the aim would be to use this in our -- to identify assays that would identify this as a potential cytokine release inducing agent, but also use it in our investigations of PLC activation.

Thank you.

CHAIR MULÉ: Great, thank you.

Questions? I have just a brief scientific question. How will you know if the antibody and CD28

that you raise, even if it does mimic some aspects of the 1412 antibody, will have the in vivo effect? Can't you get the 1412 antibody?

DR. RELLAHAN: Yes, I tried to get the 1412 antibody, and both the innovator of it and T-Genero were not willing to give it to me. So, we'll look for one the way that -- in all three cases there's an anti-rat, an anti-murine, and an anti-human, anti-CD28 that all recognize the same region, and they all induce proliferation. So, we are going to screen for proliferation and if we need to move on from that the OTR, the Office of Testing and Research here at CDER, actually has a very good animal pharm tox, clinical pharm tox unit, and there's a possibility we could work with them in looking at cytokine release, although this would be anti-human, we'd have to do something to get it into -- recognize the murine. But, at this point we are going to use proliferation, because all the other antibodies induce proliferation.

CHAIR MULÉ: Okay. Dr. Rellahan, what is the percent effort from the critical path initiative project versus the research in specific things one and two?

DR. RELLAHAN: I would say it's probably

about 30 percent of the lab.

CHAIR MULÉ: 30, and do you usually have a time line as to when, say, the critical path initiative project begins to wind down, and you are able to then take more attention to, say, the other aims?

DR. RELLAHAN: The funding for the critical path initiative project is an annual funding allocation, so there is supposed to be projects that have -- that you can get them fairly much complete within a year.

CHAIR MULÉ: Okay. Okay, great, other questions?

Okay, let's move on to Dr. Koslowski.

DR. KOZLOWSKI: Hi. I'd just like to point out that since there may be some animations in the slides that were sent out, it would be better not to view them as slide shows, because I think over the phone that would be confusing.

So, I want to talk a little bit about my project, which is activation and migration of T cells. I came from a background looking at MHC and TCR interactions, and I've moved to look at migration.

In the second slide, it talks about project aims, and aim one is in vivo outcomes, and

we've done some work on that, but we are sort of moving to look more exclusively at aim two, which is cell surface reorganization and migration.

So, if you go to slide three, it talks a little bit about the relevance of this. So, there are a wide variety of products that are being developed to target cell migration and adhesion. Some of them small molecule, some of them biologicals, and some products may have unintentional effects on migration and adhesion. And so, we are interested in developing models that would be useful in looking at potential combination effects, and look at sort of the targets for these drugs for migration and adhesion changes, and how they might predict or not predict interactions.

If you go to slide four, so the cell here depicted as a cell that's in the process of migrating, it's organized into a leading edge, which has chemokine receptors, an (?? 3:14), and a tail or a URAPOD, in which some adhesion molecules and CD43 move to. And so, this morphology is associated with migration.

So, one of the things we noted in 2002 was that the movement of CD43 to this URAPOD or tail or cells, when they were stimulated could be blocked by

statins or drugs that block MHG co-way reductase, and they block them just the movement of the CD43, they didn't actually block the other shape changes in the molecule, which was unusual.

We've gone on to look at this further, and the bar graph on the side of that is looking at polarization using imaging flow cytometry, so this is a method where every cell that goes through the flow cytometer has a digital photograph taken, and one can then use a variety of algorithms to look at the polarization of fluorescents on that molecule, or the distribution of the molecules. And so again, here we see that (?? cyndostatin 3:16) on a very commonly used statin drug has significant effect on the polarization of CD43, and, in fact, at doses that are quite low, and doses that would be seen under normal use of this product in clinical situations.

In addition to CD43, we found that it also blocked the redistribution of chemokine receptor CCR5 and other chemokine receptors, and that correlating with this change in distribution of molecules on the cell was also in vitro migration through dual chambers with a membrane, and also in in vivo T cell migration, in which an air pouch was made and chemokine was placed, and the ability of cells to track in vivo to

that pouch were looked at.

So, if we go to the next slide, our interest in migration has also been using in vivo models in which we adoptively transfer TCR transgenic T cells and track where they go, and, in fact, found a number of years ago that T cells track to different organs and have different phenotypes in those organs, which is a striking finding, and we also have found that when you immunize with peptides versus whole antigen that the localization within the splenic lymphoid compartments is different, that peptide immunization tends to have cells in the red pulp, whereas whole protein tends to have cells migrating to the white pulp, where they should be. And, this may correlate with some of the lack of efficacy that peptide immunization has had.

If you go to the next slide, slide 7, we've also looked at other things back to MHC, which was my original interest, and some work with the diacore, and for a while our lab managed the diacore for the office, and, in fact, for labs outside the office.

And, if we go to the next slide, we are also involved in regulatory work and have published on regulatory issues.

And, if we go to slide 8, and we've given talks about the work on cytokine polarization and migration, but also have given a large number of regulatory talks and workshop panels over the last few years, on issues like biological activity, follow-on proteins, and protein manufacturing.

If we go to slide 9, this is something Dr. Clouse mentioned. So, pretty much since a few months after my last site visit, there have been a lot of changes in my administrative responsibility, from becoming a Lab chief, to Acting Deputy of the Division of Monoclonal Antibodies, Acting Director, and then Acting Director of the office, and finally, Director. And, one thing I'd like to point out, because this was something that I was questioned on rather extensively during my interviews at the site visit, was that this is a large burden, however, the burden of the transition is probably greater than a stable position. And so, my situation was, every half year to year I was learning somewhat of a different job with different responsibilities. I think now that I am permanent in my position, that the learning curve will complete itself and the ability to handle the administrative issues more efficiently will be concomitant with that.

If we go to slide 10, so to talk about current and future plans, so again, I think the plan is to focus more on the migration aspect of this, and limit the scope of the program, and certainly one of our observations with statins should be looked at mechanistically. And, the graphic here looks at some of the roles that statins can play in migration, from directly blocking integrins, although at very high concentrations, to blocking the synthesis of cholesterol, to blocking prenylation of small G proteins, which can have effects on the cytoskeleton.

And, what we intend to focus on, and again, with help from the discussions at the site visit, would be to look at specifically the role of prenylation versus cholesterol, using specific blocker as a prenylation that block for insulation, or journal group addition, and also to then look at how that might impact the cytoskeleton. And so, we've obtained some mice where with pre-locks we can delete out potential linkers to the cytoskeleton and begin to use those animals as a way of dissecting out where in the process stations, and potentially other drugs, may impact migration and polarization of these cells.

And then, obviously, the goal of this would be then to evaluate the interactions of this

with other biologics, like the monoclonal antibodies that would block adhesion and migration, and other small molecules that may not. And clearly, as many, many individuals run statins and the biologics are going to have expanded targets and other drugs are going to be developed, the role of interactions, and which ones to look for, and how to make that decision effectively and efficiently, is a very, very important issue.

If we move to slide 11, so in terms of sort of current and future plans, so we want to increase our collaborations, and we are starting the collaboration with Anna Gammero and NCI, about looking at inflammation in cytokines and cell migration, using some of the models we have. We interact with FDA's group that looks at adverse events, and trying to see whether we can link the ability to look at these interactions with adverse event databases. We are interested in forming collaborations to have more sophisticated imaging. We've done some attempts to look at polarization by things like histograms for co-localization, and they actually have not been as informative as the imaging flow cytometry, and we are looking at strategies for dividing the cells into sectors to potentially use microscopy for that

purpose.

And, we are expanding the lab into interacting more with NIH in general, by joining Phil Murphy's Journal Club on Chemokines and Cell Migration.

Administratively, as Dr. Clouse mentioned, I'm no longer acting as Lab Chief, so I have only one administrative job. Wendy Shores has been acting as Deputy and beginning to really manage the OBP research program, to free me of the details of that on a day-to-day basis, and to help manage that, and that position will be advertised to be permanent.

And, we are planning to have someone who already works with us on a detail from another office, to be an Associate Director to help with certain management issues from the program.

Okay, thank you.

CHAIR MULÉ: Okay, thanks.

Questions for Dr. Koslowski?

I just have one. Have you considered interacting with Simon Watson at Pittsburgh on some of these imaging collaborations?

DR. KOZLOWSKI: No, but certainly I'll take that suggestion. We are interested in, you know, whomever can help us with more sophisticated imaging

techniques.

CHAIR MULÉ: I would encourage you to give him a call. He is one of the experts.

DR. KOZLOWSKI: Okay.

CHAIR MULÉ: He runs the imaging core facility at Pittsburgh.

Okay, if there are no further questions, Gail, I assume now we haven't heard anymore about the open hearing.

MS. DAPOLITO: Dr. Mulè, a couple of individuals joined us. I'm just going to check on site and make sure.

CHAIR MULÉ: Okay.

MS. DAPOLITO: Is there anyone in this room who would like to address the committee on the topic at hand?

No, Dr. Mulè, so we can go into the closed session if you'd give me a second to clear the room.

CHAIR MULÉ: Okay, and I guess, Kurt, you are off then?

MS. DAPOLITO: He may have already signed off.

DR. GUNTER: I'm still here, but I'll sign off now.

CHAIR MULÉ: Okay.

MS. DAPOLITO: Okay, give me two seconds.

(Whereupon, the above-entitled matter was concluded at 3:25 p.m.)