UNITED STATED OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY

COMMITTEE

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101st MEETING

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THURSDAY,

FEBRUARY 17, 2005

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The Advisory Committee met at 8:30 a.m. in the Versailles Room of the Holiday Inn Select, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. Gary Overturf, Chair, presiding.

PRESENT:

GARY D. OVERTURF, M.D., Chair

NANCY COX, Ph.D., Consultant

MONICA M. FARLEY, M.D., Member

RUTH A. KARRON, M.D., Member

PRESENT (Continued):

PHILIP S. LaRUSSA, M.D., Member

DAVID MARKOVITZ, M.D., Member

PAMELA McINNES, D.D.S., Temporary Voting Member

ARNOLD MONTO, M.D., Temporary Voting Member

PETER PALESE, Ph.D., Consultant

STEPHEN PHILLIPS, D.O., M.P.H., Temporary Voting Member

CINDY LYN PROVINCE, R.N., M.S.N., M.A., Consumer Representative

BENJAMIN SCHWARTZ, M.D. (CPT)

STEVEN SELF, Ph.D., Member

WALTER ROYAL III, M.D., Member

MELINDA WHARTON, M.D., M.P.H., Temporary Voting Member

BONNIE M. WORD, M.D., Member

CHRISTINE WALSH, R.N., Executive Secretary

FDA REPRESENTATIVES:

KATHRYN M. CARBONE, M.D.

MARY A. FOULKES, Ph.D.

RICHARD PASTOR, Ph.D.

RICHARD WALKER

FDA REPRESENTATIVES (Continued):

JERRY P. WEIR, Ph.D.

C O N T E N T S

P R O C E E D I N G S

(8:38 a.m.)

CHAIRPERSON OVERTURF: I'd like to call the meeting to order for the second day of the Vaccines and Related Biological Products Advisory Committee, February 17th.

I'll turn the meeting over to Christine Walsh, who has some announcements.

MS. WALSH: Good morning. This brief announcement is in addition to the conflict of interest reading at the beginning of the meeting on February 16th and will be part of the public record for the Vaccines and Related Biological Products Advisory Committee meeting on February 17, 2005.

This announcement addresses conflicts of interest for sessions 2 and 3.

Drs. Pamela McInnes, Stephen Phillips, Benjamin Schwartz, and Melinda Wharton have been appointed as temporary voting members for these topics.

Meeting participants were not screened for potential conflicts of interest for the updates on

FDA's critical path initiative and the presentation on the Laboratory of Biophysics and the Laboratory of Pediatrics and Respiratory Viral Diseases.

We would like to note for the record that the agency is in the process of selecting a non-voting industry representative for this committee.

That ends the reading of the conflict of interest statement. Dr. Overturf, I turn the meeting over to you.

CHAIRPERSON OVERTURF: At this point we are going to open the meeting to the open public hearing, and before we have any members read, I'm going to read into the record the open public hearing announcement.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To insure such transparency at the open public hearing session of the Advisory Committee, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the 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 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 relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

We have one speaker in the open hearing, and I apologize if I don't pronounce this completely right. Ms. Sadhana Dhruvakumar will be representing the People for Ethical Treatment of Animals.

MS. DHRUVAKUMAR: So I'm here to talk to you about the reduction of animal years in the critical path to vaccines specifically. You know,

PETA is definitely interested in reducing animal use where we can, but I'm glad to say that the FDA also is very interested in this, especially within the context of the critical path, and yesterday I was actually meeting at the Commissioner's office covering some of these same topics and these same slides with Kathy Carbone and people from the Commissioner's office, and I was getting a very good reception, and I think that there is a lot of resonance with a lot of things that are going on with the critical path in terms of, you know, deleting some of these animal tests and moving past them.

So I'm really happy to have a chance to be here and to present some of this material to this advisory committee.

So when you talk about how animals relate to the critical path, you know, as I read that report, you know, a lot of it is about modernizing the development path, and updating outdated tool kits and moving to modern technologies, and to me a lot of that is kind of the same approach that we're taking where the animals -- a lot of the outdated took kits

consists of animal tests, and most of the modern technologies are non-animal tests, but making that transition is really hard.

The critical path, as you know, addresses three main pillars: safety, utility, and manufacturing, and you know, when it comes to safety, animal tests do not -- you know, they're problematic. They're laborious, time consuming, and we're not really sure that they're protecting us.

And when it comes to the utility, animal models, obviously there are species differences. You don't know how that relates to humans. You may be searching after targets that aren't relevant and especially when it comes to vaccines.

You know, a lot of the animal potency testing has low producibility. We're not really sure how it relates to humans, and also some of them are just designed so that they're not really relevant. You know, like when you inject rabies into a mouse's, you know, brain, it's not really a relevant route of administration. So you're not really sure what you're getting.

What you mostly are getting, if anything, is a measure of consistency of something that worked in a certain way before, but you don't really know how it relates that well to humans.

And when it comes to manufacturing, you know, there's an emphasis now more on control technologies and in-process characterization, which I know is coming across to vaccines as well, which is by nature biologicals are more, you know, variable. But if we have more faith in production consistency and more emphasis on that, I think we can reduce the batch testing which has historically been done because we didn't have that consistency, but we do need to delete those tests.

When it comes to where animals are used in vaccine development and production, you know, we do have it in the research stage, in the production stage, but most importantly and our focus is on the routine batch control testing because it is responsible for 80 percent of all animal use in the vaccine industry, and that testing, when you compare it to the whole biomedical research industry accounts

for ten percent of all animal use, which is huge. It's ten million animals a year. It's this routine testing of even a limited number of vaccines, and that's why we see it as a great opportunity.

If we can address this problem, there's a lot of potential for saving lives.

And also the other thing that causes us concern is that the biological testing has some of the most painful and distressful, you know, results to animals without any kind of pain relief, especially with the vaccination challenge type experiments.

So there's this concept of the three Rs, which you may be familiar with: replacement, refinement, and reduction, as an approach to, you know, eliminating animals and making research more humane. It was put forth in 1959 by Russell and Burch.

So when you think about that with respect to the vaccine batch control testing, when it comes to replacement, the ideal really is to get to something like antigen quantification where you do understand your protective antigen well enough and that you can

have an ELISA or something like that set up well enough to detect the right antigen and the right confirmation.

It takes understanding that, whereas a lot of the vaccines we have aren't characterized well enough. We'd like to get there, but in the meantime, also we can delete certain tests, such as things that, you know, can be deleted due to production consistency, and we don't really need it anymore. So it's another way to go about it.

When it comes to refinement, refinement refers to just making existing animal experiments less painful, less disturbing to the animals. Non-lethal endpoints is one great approach there where if you know that you've infected an animal, especially a control animal, with a disease, rather than waiting for the animal to die which could be prolonged and painful, you could identify some clinically relevant endpoint that could be used to determine the disease, such as weight loss or loss of, you know, neuromuscular coordination, and then you can euthanize the animal at that point.

But even that takes some amount of validation to understand what those endpoints should be.

And also vaccination plus serology or some measure of immune response obviously is another way where you don't have to go to the challenge, which is one of the worst aspects, and that is also considered a reduction because usually you get more quantitative data out of that and you can reduce the number of animals.

Another way to reduce is to move upstream in the production process and just focus on if you could understand your adjuvant well enough, you can test the final bulk on animals but not also have to test the final lot.

And lastly, moving from a multi-dilution traditional approach to recognizing that maybe single dilution gives us enough information.

So then I just wanted to quickly move through. You have this in your handouts. I don't want to go over all of the material, but just I tried to bring together some information that I think will

be good background material, and I'll just hit some highlights on each screen.

The USDA Center for Veterinary Biologics there, you may be aware, is doing a lot in this field. They feel like it is a real priority there both in industry and within the regulatory part.

They had a conference in April in Ames, Iowa that I attended, and there was a lot of participation. People are very interested in replacing animal testing within the vaccine industry. A lot of those people are vets, of course.

They've presented to the U.S. Interagency Committee on validation of alternative methods on some of the alternatives that they're developing, and they're also trying to do rulemaking changes and changing the legislation and the regulation itself to put the non-animal test on the same footing as the animal tests which were never validated in the first place. And they've also been doing some internal research.

The biggest thing was I thought that they see that industry doesn't have the financial

incentive, even if they have the interest to develop the alternatives, and that they have to kind of be the leader in that area.

There's also the European Center for the Validation of Alternative Methods. That's a group of, you know, about 60 people that's funded by the EU who develops and validates alternatives. So they've had a lot of workshops, nine different workshops on this issue in the last ten years, and they've actually developed and validated a lot of the tests that are out there.

And so the next two slides are about regulatory bodies where they have changed the regulations. They've accepted some new tests. They've deleted some old tests. That's in Europe and the World Health Organization.

And so these next two slides, I'm really not going to go over, but basically the point is for each, you know, what I've done is tried to divide up the vaccines, bacteria on one page, viral on the other, and then we've got the vaccine, the traditional animal test and what alternatives, and then in

parentheses which bodies have accepted them.

And what I don't have here is what CBER does, and actually I'm in the process of getting that information. It's being gathered as part of the other dialogue that I'm having, but we should hope that we can bring everyone up to the same standard, especially when things have already been validated.

And it's really important in the vaccine industry especially because obviously it's a very global industry. So if something is still required in the U.S. that has been deleted or not required in Europe, it's still going to be done because they want to be able to send it globally.

So we need everyone to accept the same alternatives.

So just my last slide is kind of thinking about opportunities for how we can promote this kind of transition and change. The FDA, I know CBER is already doing research on alternatives and antigen based systems and things like that, but we really need to really better define the pathogens, the vaccines, human based tissue engineering models that will enable

kind of human based research, define our adjuvants, that kind of thing, and where the goal is, getting to the antigen quantification and to rational vaccine design where we understand what we're doing well enough so that we don't need animals as black boxes.

We also want to be able to validate and accept already whatever was on the last two slides I showed you that's already accepted in other countries. We want to be able to, you know, make sure that those things are already accepted by CBER.

We also want to promote people switching over existing products, which I think is one of the hardest things. You've got it licensed a certain way. You have to put a certain amount of money, effort, research, and then you have to modify your license. There's not a lot of incentive for that, but somehow that needs to happen.

And I'll obviously get the reviewers and researchers, you know, up to speed as well as much as possible and for a consistency of approach.

And lastly, we want to, you know, maybe organize. I don't think there has been any, you know,

CBER workshops on these alternatives. Get that dialogue going within CBER and more guidances around these things.

And the last thought I want to leave you with was just, you know, I don't think in like 100 years we'll be using animals in the way that we are for vaccine testing. Hopefully we'll be way beyond that, but we want to get there as quickly as possible and how can we do that?

That's all I have. Thank you.

CHAIRPERSON OVERTURF: Thank you.

Any questions or discussion? Yes.

DR. SELF: Yes. My comment is that the nature of the validation that we're talking about seems to me to be really critical. When you refer to the fact that the validity of the current methods are somewhat murky, maybe some of the approaches have been validated technically, but certainly I think the connection to outcomes in humans that would be really kind of the gold standard validation has perhaps not been traced through very well.

And my concern is that, on the one hand,

that we would be replacing a set of methodologies that aren't validated in a rigorous sense with another set that aren't validated in a rigorous sense. And so in part of the proposed changes, which I think are excellent, I see an opportunity to really think through for each of these methods what really is the validation that is required and how can the appropriate studies be designed and conducted that would provide that kind of validation.

So I would in this effort like to see, you know, perhaps more effort placed in that particular area.

MS. DHRUVAKUMAR: Can I respond to that?

I think that's an excellent point. I really think it's an opportunity to improve the science, you know, as we're going about it. The only thing I would caution, I mean, this is going on in terms of validation of, you know, other types of tests that aren't related with ICCVAM and ECVAM, is you know not trying to hold the newer, non-animal tests to such a high bar that we, you know, wrap them up for so long that they can't even get out there, and also not to

use the animal tests as the gold standard for them because they aren't validated. They shouldn't have to match those tests.

But, yeah, to definitely proceed ahead, define it better, but don't try to, you know, make them 110 percent perfect before you replace something which is really in some cases very suspect.

You know, like for example the NIH test. People know that it's generally very variable and not very good. There shouldn't be that high a bar, you know, too high a bar to being considered better than that.

But, yeah, a very good comment. Thank you.

CHAIRPERSON OVERTURF: Thank you.

Yes, one comment?

DR. PROVINCE: Yes. As the consumer representative on this committee, I do have a comment. I would like to, first of all, just briefly make a distinction that the presenter from PETA did not make in her presentation, and that is the distinction between animal welfare and animal rights. I won't

belabor this point. I'll try to be brief.

But many people don't realize there is a distinction between these two, and they use the term synonymously. They are not, in fact, synonymous. Animal welfare is what we commonly think of as good care and humane treatment of animals, and I think we can all buy into that as a good concept. Everyone of goodwill can.

However, animal rights is something very different. It is a philosophy which holds humans and animals are of equal or similar value, and that I personally reject, and as a consumer representative, I feel that it is important that I bring this to the table.

PETA is such a group. It is an animal rights group. They have the right to hold that philosophy. However, I must say that as much as I could say about PETA and their actions over the years, I won't do that now, but what I will say is that although the reduction in the use of the number of animals may be a worthwhile goal, if in some doing we can simultaneously meet higher ethical obligations, I

do want to state in the strongest possible terms that our highest ethical obligations remain to the human recipients of the vaccines recommended by this body.

Thank you.

CHAIRPERSON OVERTURF: Is there anyone else who would like to make a presentation during this public hearing?

(No response.)

CHAIRPERSON OVERTURF: So I think we will close the public hearing and go on with the agenda, and the first thing on the agenda will be presented first by Dr. Jerry Weir on the FDA critical path initiative update.

DR. WEIR: Thank you and good morning.

On March 16th, 2004, the FDA released a report entitled "Innovation Stagnation: Challenges and Opportunity on the Critical Path to Medical Products." In this report was described the urgent need to modernize the medical product development process, the so-called critical path to make product development more predictable and less costly.

In this critical path initiative, the FDA

will take the lead in development of a national critical path opportunities list with the goal of coordinating, developing, and/or disseminating solutions to scientific hurdles that are impairing the efficiency of product development industry-wide.

If you're interested more in the critical path initiative of the FDA, you can find quite a lot of information on the FDA Website that is listed on this slide.

Now, as part of this critical path initiative, CBER hosted a workshop on October 7th, 2004. The short title of this workshop was "Working with Stakeholders on Scientific Opportunities for Biologic Products."

The participants in the workshop included representatives of industry, academia and other government agencies, as well as the public, and in this workshop CBER staff presented overviews of current and future scientific opportunities. These included presentations on cell tissue and gene therapies, blood and blood products, manufacturing science, statistics, risk management, and clinical

trial design, as well as vaccines.

Following these presentations, we had breakout sessions with panel discussions. So what I want to do today is basically give you a very brief summary of what we presented at this CBER workshop. Dr. Kathy Carbone, who is the Associate Director for Research at CBER, is in the audience, and she's available if someone would like to know more about the FDA critical path or the background to this workshop.

Following my brief summary of the vaccines session of the workshop, Mary Foulkes, who is also in the audience, will give a brief update on clinical trial design and other statistical issues.

So essentially what I'm going to do is just walk through and brief what we did at this meeting.

We started out in the vaccine sessions by presenting the types of laboratories that we have at CBER in the Office of Vaccines, and these are listed on the slide that you see here. In the immediate Office of the Director of OVRR, we have a Standards and Testing Section and an analytical chemistry staff.

We have two product divisions that conduct basic research most of which is on the NIH campus.

In the Division of Viral Products, we have laboratories of DNA viruses, retrovirus research, hepatitis viruses, vector borne viral diseases, immunoregulation, method development, and respiratory diseases.

In the Division of Bacterial, Parasitic and Allergenic Products, we have laboratories of immunobiochemistry, biophysics, enteric and sexually transmitted diseases, bacterial polysaccharides, methods development and quality control, microbacterial diseases, and cellular immunology, bacterial toxins, and respiratory and special pathogens.

Now, the type of research and laboratory activities that that take place in the laboratories and the Office of Vaccines are designed in part to facilitate the development and evaluation of new vaccines. We considered this an important critical part of our mission.

To do this we must anticipate and address

the regulatory issues for new products. These include very general regulatory issues which are applicable to many products or product classes. I've given a couple of examples on this slide.

For example, cell substrate issues which apply to many different products, especially viral vaccines, but also general regulatory issues, such as improved test methods, which include better sensitivity, more reliable methods that are applied to broad classes of products that we regulate.

But also to facilitate the development and evaluation of new vaccines, we have to address product specific issues. These can include things like correlates of protection that are necessary for efficacy evaluation; also include research design to improve assays that are important for our evaluation, potency, efficacy assays.

Also we have efforts for animal models for different vaccines that are necessary for efficacy evaluation.

Now, obviously to facilitate the development evaluation of new vaccines, all of our

research efforts have to be prioritized. This is because we have to keep in mind the availability of the necessary expertise that we have on hand.

We also have to consider the appropriateness of the research effort. Who should do it? Should we do it in house? Should industry be doing it? Is someone else already doing it?

And of course, as obviously you know, we have many competing demands on our time and many responsibilities, and we always have to balance that with what we do in the laboratory.

In the next three slides I've listed just a few examples of research efforts that are ongoing in the Office of Vaccines. In the slide shown here, I have some examples of critical path efforts that are ongoing in the general category of things that are applicable to many vaccines.

For example, we have several laboratory efforts ongoing and in the last few years to develop alternative lot release tests. Now, this is important because this can lead to increased product availability. It can also in certain circumstances

reduce animal testing.

And some specific examples that I've shown here are efforts that we've had over the last few years on rabies potency assays, mumps neurovirulence assays, anthrax potency, and diphtheria toxoid potency.

We've also had quite a few efforts in the development of rapid microbial tests. These are important developments because they can improve current products, as well as facilitate the evaluation of new vaccines, particularly combination vaccines. Development of new tests in this area can reduce the time and the amount of product needed for testing.

And finally, in this slide, I've listed the evaluation of novel cell substrates for vaccine production. We have efforts ongoing to develop new molecular methods to detect broad categories of potential adventitious agents, as well as the development of new assays to assess tumorgenecity and oncogenicity and to detect oncogenic viruses. All of these are important for the evaluation of many products that we regulate.

In the area of virtual vaccines, I've listed a few examples of critical path efforts that we have for what I've called priority viral vaccines. Hepatitis C, we have efforts devoted to the development of transgenic mouse models to study pathogenesis and evaluate vaccine candidates.

In the HIV field, we've been involved in the development of new assays to distinguish vaccine response from actual HIV infection, as well as the identification of target structures and epitopes for neutralizing antibodies.

In the smallpox area, we've been involved in development of improved assays to evaluate vaccine response, as well as the animal models necessary for the evaluation of new vaccines.

For West Nile virus, development of standardized immunological assays for vaccine induced immunity. Poliovirus vaccine, the development of animal models to evaluate efficacy of Sabi-derived IPV which could become more important in the next few years, and of course, influenza vaccines. We've been heavily involved in the development and

standardization of reference strains and reagents for the evaluation of regular interpandemic as well as pandemic influenza vaccines.

Some examples of critical path efforts that we have for priority bacterial vaccines include several efforts in the anthrax area, development of animal models of pathogenesis, development of serological assays, development of Ty21a vectors for protective antigen, and of course establishing tools for genetic manipulation of a pathogen.

In the tuberculosis area, we've been involved in the discovery of novel antigens with protective properties, as well as the evaluation of DNA vaccines.

Shigella, the creation of Ty21 vectors for Shigella LPS.

In the pneumococcus area, identification of the serological correlates of protection.

Meningitis, the development of high efficiency conjugation technology, a well as establishment of correlates of protection.

So to summarize what we presented at this

workshop, the Office of Vaccines recognizes that there are numerous scientific, technical, and regulatory challenges that must be addressed in the development of new and improved vaccines. These include general regulatory issues, as I've tried to point out, as well as very product specific issues that we must address.

I've also as a subheading listed that we all face the challenge of vaccine development for emerging diseases.

We think that OVR researcher reviewers have a major role in identifying and anticipating such issues. It's up to us and it's one of our major responsibilities to provide clear guidance regarding the expectations for product development and licensure.

As an example of this I've listed our involvement in producing and distributing guidance documents. For example, revised cell substrate guidance documents, as well as DNA vaccine guidance documents are some that we've worked on in the last few years.

It is also, we feel, necessary that CBER

research activities are important to address these issues with regulatory implications. This is both important for product development and product evaluation, and if you think about it, product evaluation is part of product development.

Okay. So in the afternoon, we had a vaccine breakout session and a panel discussion. I want to summarize that in the next two slides. Our list of panelists for the vaccine sessions included our own Dr. Overturf from the University of New Mexico; Alan Shaw from Merck; the late John La Montagne from NIH, the Deputy Director of NIAID. We had Robert J. Reinhard from the AIDS Vaccine Advocacy Coalition, as well as Laurie Norwood from the CBER Office of Compliance and Biological quality.

Each of these panelists started off the breakout session by providing their own perspective of the entire vaccine development process. The floor was then opened to discussion, and we had a brief summary of this discussion that was presented to the larger group when we reconvened.

So, in short, I've listed a few of what I

thought were the overall themes of this breakout session. In general, the panel felt that the entire process of vaccine development should be reengineered. I actually that if I remember correctly, this was John La Montagne's phrase, but almost everyone in the room agreed that there were just many aspects of the current process of vaccine development that were not optimal.

These included complex and cumbersome IRB process, the burden of data management, the lack of sharing of information about trial design, and again I remind you that these are not CBER specific issues. These were just issues related to the whole process of vaccine development.

Many in the audience and the panel thought that there was importance of establishing and validating surrogate endpoints for vaccine trials. Everyone emphasized the importance of communication both for CBER and for the Office of Vaccine to provide detailed guidance for industry, but also there was a feeling that there should be more guidance for those with limited experience in the vaccine development

field.

There was general consensus that there should be more long-term follow-up and post licensure surveillance.

There was also general consensus that CBER research did have a major role and can assist in vaccine development. Topics that were specifically mentioned included more preclinical studies, studies on novel antigens, studies on adjuvants, vaccine delivery methods, as well as just the overall rational vaccine design, including defining surrogate markers.

Finally, the next steps in this process. For the FDA critical path initiative, we will continue to compile an opportunities list. There will undoubtedly be additional workshops on specific diseases, products, and pathways.

For CBER we will summarize and publish the discussions from the CBER workshop that I have summarized, and we will use this information to develop future CBER science priorities and agenda, and of course, we will continue to try to communicate scientific advances in guidances, policies, and

publications.

And as I said, Mary Foulkes will now give you an overview of the statistics and clinical design.

DR. FOULKES: Okay. Thanks, Jerry.

Okay. Thank you very much.

As Jerry mentioned, I'm Mary Foulkes from the Office of Biostatistics and Epidemiology, and at the same workshop that Jerry mentioned, we had a breakout session on statistical issues, risk management, and clinical trials design, and I'm not going to summarize that in great detail, but I'm going to give you more of sort of a holistic look as to how we approached the critical path.

I don't often get a chance to quote Pasteur, and so I'm going to take that opportunity. I really think that this quote, "Chance favors the prepared mind," consolidates the entire critical path opportunity that we have here, and another reason that I have for pulling this particular quote is that "Chance" is the name of one of the regular publications of the American Statistical Association. So it caught my eye for that reason as well.

If my theoretical statistical colleagues will forgive me, I'm going to wildly oversimplify the usual statistical approach to development of methodology. Usually there is a highly mathematical development of the theory or a new model or a new method, and then there's a search for an application to which it fits.

Well, we see the critical path approach as really upending that process and identifying areas where there exists no prior approach or no existing approximation as a part of vaccine development or biological product development and developing a mathematical or statistical methodology that fits that need and finding a methodology because there is an application searching for a methodology.

With regard to the quantitative methods in general, we see the need as the whole critical path concept maximizing efficiency while maintaining reliability, and certainly within vaccine development there are many opportunities to approach that by certainly improving the analytic approaches and by, as was mentioned by Jerry, flexible study designs, and

I'll get into that a little bit further.

Also, there is a need for a transparency, for education of, as Jerry mentioned, of vaccine developers, for example, who have maybe less experience than others in the process.

Also, transparency in terms of determining best practices for quantitative methods. In some instances there are multiple practices available, but the particular best practices have yet to be identified, and really the field is using a lot of variation in practices without establishing a best practice.

There also needs to be transparency in underlying assumptions. A lot of the quantitative methods are based on assumptions or start with various assumptions at the beginning of the process and are dependent upon those assumptions. Sometimes they are realistic assumptions. Sometimes they're simplistic assumptions, and so there is an opportunity there to possibly improve the product development and the contribution of quantitative methods.

The list of CBER products I know you're

all familiar with. With regard to vaccines, in particular, the critical path is important because many vaccines are available to a huge target population many, many times larger than the available data set for evaluating that particular product for safety and efficacy.

Vaccines, when they are made available, are administered to healthy people. They're also often evaluated in healthy people, and that has implications for the risk-benefit assessment. Vaccines, when they are at all effective and available publicly and universally and worldwide, can have a major public health impact, as we all know, and again, as we all know, there is a growing public safety concern, and just the existence of a safety concern can impact vaccine coverage rates.

So it's very important to address those. So some of the things that Jerry has already mentioned, and I'm not going to go into great detail in these, but some of the areas in which quantitative methods can have an impact in improving product development and in the entire critical path process in

terms of study endpoints.

And here's a short list of potential study endpoints, all of which have implications for quantitative methods and for analytic approaches and for the kind of inferences that can be made from them. And those need to be assessed in a critical path context to see if there aren't any opportunities for improvement in the definition of the study endpoints and also in the analysis of the study endpoints and the inference from those study endpoints.

Genomics and proteomics is a very large and rapidly emerging area of research as can be seen by the huge emphasis on genomics and proteomics this weekend at the AAAS meeting downtown, which actually starts today downtown.

The statistical practices for these areas are not yet well established, and this is definitely an area for potential development. There are lots, as you can imagine, multiplicity issues, multiple plates, multiple SNPs, multiple everything. There are lots of potential missing data issues. There are missing data issues elsewhere as well, but particularly in the

genomics/proteomics area, how one handles missing data in terms of the analysis is very important. And there are certainly experimental design opportunities in this context.

There are statistical issues in manufacturing. Particularly recently we've been dealing with issues of quality control and blood collection, but there are also specific manufacturing issues related to vaccines, as Jerry has already mentioned, vaccine lot consistency.

Now, the flexible design issue. There are opportunities to consider alternative experimental designs, clinical trial designs, and these have been widely under discussion. For example, there was an FDA workshop just this spring. Sorry. It was 2004 on flexible design, on adaptive designs. Adaptive designs, again, are being discussed at the FDA Science Forum, and it's a very active area of research.

The reasons that one might consider flexible design in the context of vaccine development or any product development is that sometimes when the product development process is speeded up a bit, there

might not be a lot -- the amount of learning curve that precedes, say, the Phase III clinical trial is compressed such that your estimates of the initial parameters for that Phase III clinical trial design might be less solid than we would prefer.

And so there may be opportunities for interim modifications to the ongoing design. Those have to be handled very carefully and planned for and have implications for the analysis and the interpretation. So it's an area that is currently enjoying rapid development.

There are also the traditional approaches, the group sequential designs, and so forth, and there are new emerging approaches to consider. But this is a very active area for statistical methodologic research, and the specifics of flexible designs for biologics are obviously CBER regulates cutting edge products, and as I mentioned earlier, we may have less information going into a Phase III design than we might want, and we have the need for flexibility as the Phase III clinical trial is progressing.

Again, safety concerns. There may be a

safety concern that emerges in the course of a clinical trial that has impact or could have impact on the trial design, and a flexible design might give the opportunity to handle that.

With regard to trial design and analysis, there are opportunities for improvement in the process, improvements in handling non-inferiority trials, for example, and obviously the ICH E10 already exists and gives us guidance in that arena, but there certainly is room for improvement in the methodology there.

There is a lot of room for improvement and activity. There's a lot of activity in terms of handling missing data in analyses. As with other areas of analyses, there are multiple opportunities and multiple routes that one might take, but there is no really identified, necessarily preferred analysis approach. And so there's an opportunity for improvement here.

With high speed computing there are also opportunities for handling missing data utilizing the high speed computing capabilities that we didn't have

ten or 15 years ago and we have in our tool box today.

Another area of methodologic development is data mining, and here CBER and other have been using empirical based methods to try to apply those to, plus marketing surveillance, and utilize the information that we get reported on adverse events to identify areas of research and of concern with regard to vaccine safety, in particular.

This can be problematic because obviously false positive signals could have very serious consequences, and so one has to utilize this information very, very carefully and take into account the fact that it's based on our adverse event reporting system, and other sources like that where under reporting may be a serious problem. So that always has to be in the back of your mind when analyzing these sorts of things.

Let me go straight through to the summary. We're approaching issues of risk analysis. This is an area where obviously we are in situations where we have to make decisions, and the decision point comes in not necessarily as a function of having complete

data in front of you.

So often you have to make decisions in the absence of full information, and this is where risk analysis can play a role. One can model the risks and identify influential parameters where we can put our resources to clarifying those parameters, getting more information on those parameters, possibly directing resources to gain more information in that arena.

So this is an area of development and an area that the critical path can consider as part of its armamentarium, if you will.

So, in summary, the quantitative sciences need to be considered as a part of critical path, and have a role to contribute to improving the process of product development and contributing to the critical path in terms of the quantitative methods that I've outlined.

And just in summary, that statisticians and epidemiologists need to be involved just as much as anybody else in the identification of issues and encouragement of involvement in development of new methodologies that improve product development.

Thank you. Any questions?

CHAIRPERSON OVERTURF: Are there any questions or points of discussion? Yes, Dr. Self.

DR. SELF: I can't resist. Dr. Weir's slides mentioned in his summary of the panel discussion the importance of establishing and validating surrogate endpoints for vaccine trials. There's been a lot of that work that's been done in other settings and without the most optimistic results for actually achieving that. That's not something that is in your presentation. Could you just give a couple of minutes thinking about where that sits with respect to vaccine?

DR. FOULKES: Well, certainly, as I indicated in the list of potential study endpoints, that study endpoints need to be evaluated very, very carefully, and whenever we talk about surrogate markers, I always have the tape of one of Dave DeMets' presentations in my head where he has multiple, multiple examples of how we were misled by various surrogate markers particularly in the field of cardiology, which is the source of many of his

examples.

So we have those caveats in mind always, but there certainly is a potential for surrogate markers, intermediate endpoints, biomarkers to be utilized should they prove valid sources of information and valid bases on which to make regulatory decisions, but that's a very large "if."

DR. SELF: So a comment, and then one sort of small question.

The comment is even though your talk is targeted at clinical trial design, I guess I would like to see the range of issues broadened to include preclinical studies as well because that is a bridge that has not been built very well and really needs to be. So I just raise that on the radar screen.

DR. FOULKES: Absolutely. The intention is not to exclude those.

DR. SELF: Yeah. And then I found myself scratching my head a bit, and maybe this is to Dr. Weir, in the reengineering of the vaccine development process. Listed here as Item No. 2 is burden of data management. I don't know what that means.

Could you or somebody explain that one?

DR. FOULKES: Jerry, if you want to, take that, but I can jump in at one point that there is a perception, if not a reality, and it probably in many cases is a reality, that the burden of data management is too much of a burden, and I do think that there is room and opportunity within the critical path. In fact, this was one of the discussions in the breakout session that the individual data items that are captured and collected and edited and stored and constitute that particular burden need to be reevaluated in terms of do we need this particular item and why do we need this particular item?

And I think there is a lot of room for improvement there. There is a lot of room for efficiency, and os let me let Jerry jump in.

DR. WEIR: Well, I think you just summarized it. That was the general feeling of several people in the group, was that it was just an overwhelming amount of data.

And I think I remember that some questioned whether all of the data that was asked to

be collected was really necessary, and they talked about not only just the sheer amounts, but how you manage it. So it was just sort of a general feeling that it was just a big burden in the running of large clinical trials.

But like I said, I think May summarized it now.

DR. FOULKES: May I just add that the FDA for a number of years now has been discussing large, simple safety trials, and one of the emphases in that discussion is the reduction of the data collected to what is absolutely necessary.

Another quote that I cut out of this talk is "make it as simple as possible, but no simpler." And I think that that's an area where we can make some improvements with regard to data management.

CHAIRPERSON OVERTURF: Dr. McInnes.

DR. McINNES: Thank you.

I also was having a dagger through my heart around this thing about burden of data management, and I guess I understand a little bit better. It's around, I think, the issues or challenge

of appropriate data collection and then superb management of those data that are deemed to be important, and I think we struggle so much with this with all of the contractors and grantees who some resist the fact that this is now 2005 and it's perhaps just not okay to have handwritten data in your lab book.

I mean, we are now in the very contemporary area and things have moved on. So I presume the burden issue is really around the challenge of appropriate data collection and data management.

I'm interested in the proceedings that come from the panel because I think certainly with multi-center studies and with emerging disease issues where you may only be capturing a few subjects at a large number of medical centers, for example, the current IRB process is really very challenging in trying to implement these multi-center studies, and I really think that's an area that we need to tackle very seriously and together because it is proving to be very difficult and impeding enrollment into very,

very important studies.

I also wanted to just make a pitch again, I think, the lack of specificity around terminology of correlates and surrogates. While there's a very small number of people who really understand the difference between correlates and surrogates and some of those people who got burned in those cardiology studies, I think these terms are tossed around quite freely and people talk about correlates of protection and not necessarily understanding that there may be some endpoint that you're measuring that has a relationship to what you want to look at, but that you can't just measure A instead of B and assume that it's a true surrogate.

And I actually make a plea to this committee. Maybe even some publication that could go back to definitions of correlates and surrogates and something about what it really is and what it isn't, in that I think very often we are measuring correlates and not necessarily surrogates. I think this vaccine development arena could really benefit from some of that work that has been done really in drugs.

So thank you.

CHAIRPERSON OVERTURF: Dr. Schwartz.

DR. SCHWARTZ: A comment and a question. In the statistical presentation, you talked about using data mining techniques and Bayesian analyses and all of that. At CDC they're obviously looking at the same things, both with respect to vaccine safety as well as outbreak detection. I don't know if you've been working with the statisticians at CDC --

DR. FOULKES: Yes.

DR. SCHWARTZ: -- but clearly, linking with other government scientists would be useful for that.

The question is at the end of Jerry's presentation it was mentioned how this new information would come out in policies, guidances, publications, and there were a lot of different aspects of the critical path that were talked about, and I'm just wondering whether the vision is that as individual issues were addressed there may be a particular guidance or particular publication about that individual component of the pathway or whether it's kind of an end-to-end thing where there would be some

kind of guidance that would deal with the full range of issues.

So how do you see this coming out when decisions are made, when new approaches may be validated? What will be the way that then this will be translated into action in terms of vaccine development?

DR. WEIR: I'm not sure I followed the question, but were you referring to how we would decide to publish guidances on specific topics?

DR. SCHWARTZ: Well, I guess just more clarity. There was such arrange of topics that are being reviewed. Is this something where you would, when a particular topic was addressed, you'd come out with a guidance or a publication on that specific topic, or would it be to complete an entire kind of end-to-end review as it were and to put it all together then?

DR. WEIR: Okay. I would have said the specific topic, but I think Kathy wants to --

DR. FOULKES: I think I understand what you're getting at. These are all major issues that

are somewhat separable, and they all have scientific knowledge gaps and tool gaps, et cetera. So as the information comes across for a particular area, that would come out as a guidance.

So it might be an issue with a particular vaccine, a vaccine type, a type of product, and as that information is gathered, it will come up as a guidance, and keep in mind guidances are living documents. So even as more information is gathered, the guidances will be updated so that the concept is to feed very quickly into the regulatory pathway and make the advances clear as they come along.

CHAIRPERSON OVERTURF: Are there any other questions?

I just wanted to make one comment. My impression from the workshop was that a good number of the identified difficulties in vaccine research were, if I could use a term, were pre-FDA, I think, or post FDA, but they really didn't center there. They centered in places like local IRBs, the recent expansion of HIPAA regulations and other kinds of problems which have really had a tremendous

disquieting impact unfortunately on particularly collaborative research in vaccines.

And it has not only been in vaccines, but it has obviously been in other drug research as well, and I think one thing the critical path might want to do is to really look deeper into and expand into those areas because I don't know how the FDA could impact those areas, but that would be an area that might facilitate more research more than just about anything that I know of right now because those are the major problems. Because it starts right at your own institution usually.

Were there other points of discussion?

We have to take a break because we have to get Dr. Palese on the phone. So is he expecting to be available precisely at 10:05?

MS. WALSH: No, I told him a little earlier.

CHAIRPERSON OVERTURF: Okay. So how long do you want us to take a break?

MS. WALSH: Ten minutes.

CHAIRPERSON OVERTURF: All right. So

we'll take a break and be back at ten minutes till ten.

Okay. Thank you.

(Whereupon, the foregoing matter went off the record at 9:35 a.m. and went back on the record at 9:55 a.m.)

CHAIRPERSON OVERTURF: Please take your seats because we have Dr. Palese on the telephone, and we need to begin the open committee discussion and presentation of two laboratories.

The first presentation will be an overview of the Laboratory of Biophysics and will be presented by Dr. Richard Walker.

DR. WALKER: Good morning. Actually for the next few minutes I won't present an overview of the Laboratory of Biophysics, but I'll present an overview of the Division of Bacterial, Parasitic and Allergenic Products, which Biophysics Lab is a part, and so I'll try to give you a big picture, and then Dr. Pasteur can go into the details of the Biophysics group.

What I'd like to do is sort of hit three

things: give you a little bit of discussion of the challenge that our division has to face, the way we're organized to meet that challenge, and then a little bit about sort of what it's like to be a researcher or reviewer within this division.

Okay. So our laboratory function, as you would assume, is to assure safe and effective products for immunological control of bacterial, parasitic and allergenic products that affect human health.

Our task to do this involve research, as well as review. That's why we refer to our personnel as researcher/reviewers. We are involved not only in new products coming in, but also post licensure surveillance, and also we are involved in many consultations with organizations that are developing vaccines, as well as NIH and other organizations that are dealing with various vaccine problems.

This slide and the next slide are really not to go through all of the details of what's written, but just to make a point that when our researcher/reviewers begin working with a product, we take it from the beginning through the end. So it's

a lifetime arrangement from pre-IND, where we might have a pre-IND meeting to help the sponsor work out problems, to receiving the IND, a review of that, technical advice for development of product assays and so forth.

Then we go on through the clinical testing, the licensure process, continuing back-and-forth dialogue with the sponsor, and then in the post licensure, our work is not over. Like I said, it's a lifetime arrangement when we're working with a vaccine or other immunological product.

The types of agents that we have to deal with, as you can get from the name of our division, is very varied. We have respiratory pathogens, sexually transmitted pathogens, other things like malaria, special pathogens which really received a lot of emphasis recently, those that could be bioterrorism agents.

We also have diarrhea causing pathogens, other types of pathogens. If you look back, for example, to allergenic products and skin test antigens. So see we have a variety of things to deal

with, and to do that, we have about 90 people in the division, and we're organized into eight laboratories. So we have the Office of the Director with my administrative and regulatory staff, and then we have the various labs.

Two of the labs, this being one, the Laboratory of Methods Development and Quality Control, are more approach oriented. The other six labs are more disease oriented. This first laboratory deals with things like methods for quality control and serological assays, their development in animal models, and they deal right now a lot with pertussis and anthrax.

The Laboratory of Biophysics, which you're going to hear a lot more about in a few minutes from Dr. Pastor, brings new techniques that allow us to do cutting edge evaluation of vaccine products and understanding of the chemistry of these vaccine products.

Now, these other six laboratories are more pathogen or disease oriented. The Laboratory of Bacterial Polysaccharides is actually just one that

the Laboratory of Biophysics collaborates a lot with because a lot of the technology like NMR and so forth that Biophysics has is very beneficial to the people in this laboratory. Anyway, they're interested in characterizing the immune responses to polysaccharide conjugate vaccines, standardization of methods, development of new chemical methods to understand the chemistry of these vaccines and also we've got some vaccine development studies going on there.

Laboratory of Bacterial Toxins is, of course, another major area because we have botulinum toxin, tetanus and diphtheria. So we have to have experts dealing with those various toxin products.

I'm not going to go through the details of these unless you want to go back to that. I'm just trying to give you the overview.

Laboratory of Respiratory Special Pathogens, which is looking at virulence factors and regulation of these virulence factors for things like plague, anthrax, and pertussis.

Laboratory of Microbacterial diseases and cellular immunology is dealing with various promising

antigens that might be useful against microbacterium, as well as understanding the immunology of that disease. There's also work in this group dealing with tularensis.

Laboratory of Enteric and Sexually Transmitted Diseases primarily deals with various enteric pathogens, like during the critical path thing you heard about, Ty21a vaccine being a vector for Shigella. That's some work that's going on in that group.

Laboratory of Immunobiochemistry, studies allergen structure and function in the immune responses to various allergens and trying to better understand processes in allergen activity, as well as they do a lot of lot release work.

So that's in a nutshell the division that we've put together to address the bacterial and parasitic and allergenic products.

I mentioned that we have about 90 percent in this division. I put this chart in because one of the things that these site visit committees are asked to do is evaluate the people, and so as part of that

it's helpful to just sort of review how people are sorted out or what terminology we use.

We have sort of independent and non-independent pathways that people can take and move up through various grades. One is over here on the left where you start with staff fellow. This is moving towards a tenured position to be a principal investigator, and these people are reviewed by the site visit committees and tenure will be impacted very much by the comments of the site visit committee as far as how they evaluate the work of these people.

We also have another track for people who do not plan to be principal investigators but are very capable of researchers in their own right, and they're the support scientists and the staff scientists.

One of the issues that we deal with is the funding for this research because in addition to review, in addition to having facilities to do that, we have to have laboratories and we have supplies and all of the things that go along with research.

Salary and overhead is part of base funding. What actually comes down to us at the

division level is really operating money for expendables and equipment. We have a general FDA appropriation which is really our division operating funds, and we distribute that really on a per capita basis.

Recently we've gotten counter-terrorism funds. Those funds were useful in the last few years in actually adding to our staff to be able to have a response to the issues of plague and anthrax and some of those other bioterrorism agents.

Unfortunately, we've ramped that program up, but money to support those programs has not really stayed with us, and so a lot of that now comes out of our operating funds.

There are some extramural funds like the National Vaccine Program Office and a few other sources maybe through CREDAs and some work that our people have to get outside money. In fact, right now, most of our research money is coming from the outside rather than these FDA funds.

In the past we've had some money left at the end of the year, but that's also a dwindling

resource. So I'm just painting the picture that we still have excellent people, and I think as many of you know, they're doing high quality research and are turning out very valuable information and really contributing to the scientific field, but they're doing it on a shoestring.

Other challenges and realities that face our researcher/reviewers, and some of these may be true for other government, like NIH and so forth, the funding levels are uncertain from year to year, and we have to depend on the appropriation process. We're a very large organization, and like any large organization we have bureaucratic hurdles, and also we have to try to make sure that we don't have any appearance of a conflict of interest. So we have to be very careful. Sometimes it makes a lot of paper work, and it keeps me busy.

The other thing though is, of course, at the university and anywhere else, you have other things like various committees and whatnot that take your time, and bureaucratic hurdles. One thing that's very unique that you should be aware of with relation

to our researchers and viewers at FDA is that their schedule is not totally capable of being planned by them because timing of the work load could be determined to some extent by the sponsor.

We don't know when something is coming in, and ten we have to respond to it and deal with it. So that's something that's a conflict that anyone who does research and review work at FDA has to deal with. So you have to be able to juggle.

So just to wind up, what I asked the site visit committee to do is in this case for the people in the Laboratory of Biophysics is to review the individual, the overall program, and then make comment on their current and future directions.

So if there's any questions or clarifications you need now I can do that or we can move on into the Laboratory of Biophysics. Anybody?

CHAIRPERSON OVERTURF: Are there questions now or should we just -- I think we'll proceed on to the overview of the laboratory.

DR. PASTOR: Thank you.

This is going to be a brief overview of

the Laboratory of Biophysics. You all have these giant books if you chose to read them with like more details, plus your handy-dandy disk of the whole thing.

The first slides are going to be more or less what I spoke about in the first part of my talk, and then at the very end I'm going to go into a little bit to summarize the rest of the talks.

The Laboratory of Biophysics basically has four sections. There's a computational biophysics. I'm the leader of that part. I'm Pastor. Rick Venable is in it, as well as a postdoc. Then there's a mass spectrometry and a protein chemistry section, a spectroscopy which is NMR and light-scattering, and then an NMR theory part.

And broadly speaking -- and I'll stay broad for a couple of slides and then be more specific -- we basically use these tools for a biophysical characterization of proteins and peptides, carbohydrates, DNA, membranes and micelles, essentially all of your cellular components, and this has application to everything that CBER regulates:

vaccines, blood and therapeutics. Basically we work with almost everyone, and just a couple of examples which you'll be seeing later of some of the molecules we do.

And as I said on the first slide, we use these tools. We have an array of actually mass spectrometers, NMRs up to 700 megahertz, which is quite a good machine, light-scattering, and modeling.

And the characteristic that these things all have in common is that they're high tech things. We use them center-wide, and to really use it, you have to be an expert. Your average scientist can't walk in and start using a 700 megahertz NMR. I mean partly because they're $1.3 million. So you're not going to mess with it. "Can I touch this?"

"No."

And just kind of briefly, what is a characteristic of these methods? You can read them or look in the book more. Basically mass spectrometry gets the masses of each fragment. It works very well on large proteins and mixtures. NMR is really used to actually get the structure and conformations of

molecules. Light-scattering get sizes quite well, and actually works with very large mixtures. A simulation gives you detail.

And this last column is really sort of an interesting column in that it's like, well, any technique, there are some things that you get, but some things that you actually don't get from it, and we've tried to arrange the lab so that you can almost pick your column and say, well, gee, you can't measure a large range with NMR, but in fact, using light scattering you can.

So, in fact, we've made a lot of effort to make sure that these techniques are complementary. In fact, often we'll use several of them on the same problem to map out the whole shebang, as well as research, which you'll hear about in a little bit.

We actually do a lot of regulatory work. I'm involved in the LAL test kits and adjuvants, as are Boykins and Bull and Rick Venable, and then each person -- you can read this -- acts as a consultant often in INDs or PLAs or as things come up on these issues, and that's quite frequent.

I just step back and just remind you. This is the risk analysis part of what we all think about. You know, what are the four things that could happen with a product at lot release? And it's, you know, a good product passes. A good product fails. A bad product fails and a bad product passes. That's your basic matrix.

And of course, this is the sunshine one when the good guys get passed and the bad guys get failed, but of course, it actually can happen that occasionally, and you try to work against this, but real life says it's not perfect. You will have good product failing. A lot release test gave the result that passed or that failed. That's the alpha, right?

And likewise a bad product will sometimes sneak in. And to sort of not realize that and think about it can lead you astray, and you know, what's biophysics for? Well, essentially if we understand these products better, if we make the tests better, we can reduce those risks.

So I think it has to start off with saying they're like our risks. What are they, and then by

doing a better job writing the biophysics in this case, we can lower those risks.

A site visit, this was the schedule of the people. This is a list of the people who spoke at the site visit, and each guy -- we're all guys here. So we don't have to -- spoke about his area of expertise, and I spoke about the membrane research I did, and in this slide I basically want to sort of target in some since highlight as it regards vaccines. We do other stuff, but this is Vaccines Advisory. So you get vaccines.

So I think one area that I've been working on, a large part of my research since I came to CBER has been understanding how to really on a computer simulate pure membrane. We're actually very close to that now. You know, I showed results that show we just about know how to do it.

So, in fact, I've started now -- people in the group have started computer simulations of the trehalose, which is a vaccine preservative, and we're trying to understand using simulations just how trehalose keeps the membrane stable. So I think that

will ultimately be where that goes, and I hope one of these days to say, well, we actually did it. Here's how it happens. Vaccines are better because of this.

Daron Freedberg, I spoke about his work on using an NMR technique called residual bipolar coupling, which is a very precise technique that one can use to look at the conformation of carbohydrates. The goal there, at least the carbohydrate part of the research will actually involve doing a very careful characterization of the conformations of the polysaccharide vaccines.

So, for example, a mixture of vaccine that has buffers or ions, it can actually change the conformation. One can see that exactly where it's changing it. It could be important.

I guess Scott Norris talked about light-scattering in general, and in fact, what they just did recently is they were able to determine the extent of like a conjugation of the meningococcal conjugate vaccine with light scattering, but that data was used to help justify a Gates Foundation grant by the polysaccharides group, and they got the money. So

that's actually working.

Tom Bull spoke about a method that we worked out in the lab. For the first time we were actually able to detect, you know, hydrogen bonding in a peptide directly, not because it looked like a helix in CD, and in fact, we're applying that to carbohydrates now.

Rick Venable, among other things, spoke about some conformational analysis he did on the meningococcal polysaccharides.

Bob Boykins, the mass spec guy, and he's a protein chemist spoke about his work and multiple peptide conjugates unlike malaria and anthrax vaccines.

So you see from this slide, it's kind of busy now, but I hope it wasn't so bad hearing it, how we're trying to take these really high powered methods and actually solve problems in like vaccines. So we do a lot of basic work, but we're, you know, applying it to real live vaccines.

I want to talk about one other area. In the first slide I had said that the work is CBER-wide.

Well, this is an example of that. In fact, it mostly happened sine the last site visit. So it's hot news. We worked with the blood guys, and they had problems in these blood substitutes. Some weren't working, and so we applied all of the tools in the tool box that were appropriate, mass spectrometry, modeling and light-scattering, and one really cool thing was this. When they were cross-linking that hemoglobin with raffinose, the way that's supposed to work -- at least the manufacturer said it would bind to lysines, and it turns out it just wasn't working. I mean it was just all messed up.

And so using mass spec, Boykins actually found fragments in which this raffinose wasn't just binding to lysines. In fact, it was binding to a cysteine right near the, you know, heme pocket.

And Rick Venable, the modeler, then actually placed a cysteine where it was bound, and said: well, you know, how close to this heme pocket is it? What could it do? The water is changing, you know, and then you minimize it.

And you know, to make kind of a long story

short, you can really understand how this would keep that molecule from actually undergoing the oxygen binding transition, you know, T to R, and you know, they also thought it through, and it really could explain how by perturbing that region of the molecule you can accelerate release of iron and the degradation of the heme, and that might actually, you know, give an underlying molecular basis on why this thing is toxic.

So that's what we did there. There were two papers that came out of that. One is already in press. So you see the biophysics is highlighted in red. The blood guys are important, too, you know, in biophysics, right?

So the first one is the one I just spoke about. It was with Bob and Rick. There's a second one where we use light-scattering, and that's submitted. So I'm actually very excited that the lab is work in this way now.

The last basic slide is the one thing that you have to make a vote on. I guess you can vote on lots of things, but this I really want you to vote on.

A personnel action is a promotion of Rick Venable from a GS-13 to a GS-14.

I'd just like to say that he's an outstanding scientist. He's been with the lab since 1985, almost 20 years, and he trains the postdocs. He's been working with like me on membranes. On almost all of my important publications on like membranes have been with him.

He actually provides computer modeling for anyone in the center who wants it, as witnessed by that last slide I showed you, and he has his own program and a conformation of carbohydrates. I just said, "Well, you do this. You can do it."

So he's working as a PI in that regard even though he's not formally a PI. In fact he just did a paper with the carbohydrate guys and the thing to know is like my name is not on that paper.

He does a lot of other things at CBER. He's a manager of the network, you know, takes care of a lot of things, and then on NIH he's actually an extremely well known guy. He supports CHARMM, which is a computational package that's used everywhere in

the world basically.

And lastly, he hasn't gotten a raise in over ten years. I think he deserves one.

So thank you very much. Do you have any questions for me or for Dr. Walker?

CHAIRPERSON OVERTURF: Are there any questions regarding the Laboratory of Biophysics?

DR. PASTOR: Well, I thank you very much.

CHAIRPERSON OVERTURF: Thank you, Dr. Pastor.

The next presentation will be on an overview of the Laboratory of Pediatrics and Respiratory Viral Diseases, and that's by Dr. Jerry Weir again.

DR. WEIR: Thank you.

On November 9th, 2004, we had a site visit of several research programs in the Division of Viral Products. To give you a quick background of the Division of Viral Products, there are seven laboratories. I think I've listed them already once today, but I'll do it again.

There's the Laboratory of Hepatitis

Viruses with Steve Feinstone as the Chief; the Laboratory of Vector-Borne Viral Diseases with Lew Markoff as the Chief; the Laboratory of Retrovirus Research, Hana Golding; Laboratory of DNA Viruses with Andrew Lewis; the Laboratory of Pediatric and Respiratory Diseases with Roland Levandowski as Acting Chief; Laboratory of Immunoregulation with Ira Berkower as Chief; and the Laboratory of Methods Development with Konstantin Chumakov as the Chief.

To summarize briefly the mission and the functions of the Division of Viral Products, we regulate viral vaccines and related biological products, insuring their safety and efficacy for human use. Part of our mission is also to facilitate the development, evaluation and licensure of new viral vaccines that positively impact the public health.

In support of this mission, we have numerous review and research activities. You've probably heard some of these before, but briefly we review investigational new drug applications, biologics license applications and supplements. We're involved in lot release review and sometimes testing.

We have extensive post marketing activities. For an example, I've listed biological deviation reports. We participate with the others in CBER in manufacturer inspections, and we actually have an extensive role in consultation with other public health agencies, such as WHO, CDC and NIBSC.

The research activities that are ongoing as part of our seven laboratories span the spectrum from very applied to very basic. Examples of the type of research that we perform include studies on viral pathogenesis, vaccine safety and efficacy, including cell substrates, vaccine and viral vector evaluation, studies on the correlates of protection that are necessary for our evaluation, reagent preparation, as you've heard this week, influenza vaccines, methods development and evaluation, and research efforts to vote it to emerging issues, for example, BSE, counterterrorism, other things that come on the radar screen.

To put the research program in perspective, at the present time we have a full-time staff of about 75 in the Division of Viral Products.

The entire staff of the division, counting mostly postdocs, contract workers total somewhere in the neighborhood of 110 to 120 people. We have had some recent reductions of full-time staff in FY '04 and '05.

In FY '04, we had a budget of approximately $1 million to support these researchers and these research efforts. This was a slight decrease from FY '02 and '03, and at the present time, we have supplemental funding in our laboratories from outside sources that is now substantially and significantly greater than the internal funding that we receive to support our activities.

We expect continued budgetary challenges in FY '05 as well as '06.

On November of '04, we had several laboratory teams reviewed as part of a site visit. You all have briefing documents and so I'm not going over this in detail. I'm just going to list them for you. The review of the influenza virus team which Roland Levandowski is the head of this team, but also this includes Zhiping Ye.

The major regulatory responsibilities of this group are obviously influenza vaccines, including inactivated influenza virus vaccines, as well as live attenuated virus vaccines. The areas of research and the laboratory activities in this team include the standardization, characterization, and development of influenza virus vaccines.

A second program that was reviewed in November was the viral pathogenesis and vaccine adverse reactions team. This is headed by C.D. Atreya. The major regulatory responsibilities for this group include review of measles, mumps, and rubella vaccines, particularly the rubella part of that, and also review of rotavirus vaccines which are under development.

The areas of research in this group focus on the role of host factors and viral pathogenesis, for example, primarily rubella and rotavirus.

And third team that was reviewed in the site visit is the Neuroimmunopathogenesis Team headed by Dr. Kathy Carbone. The major regulatory responsibilities in this group also are in the areas

of measles, mumps, and rubella vaccines, particularly the mumps aspect of this, and the areas of research that they focus on are vaccine neurotoxicity pathogenesis and neural virulent safety test development. One example is the mumps neurovirulence test that has been developed by Steve Rubin and Kathy in this group.

So basically on November 9th, these groups, these individual teams were reviewed by the site visit team. They were evaluated for the progress both of the individuals in each team and the team was assessed for its future directions that they presented.

And that's all.

CHAIRPERSON OVERTURF: Are there questions for Dr. Weir? Everybody has read all of those documents, I guess.

Okay. We're going to take a 30 minute break. Then we're going to come back and we'll be almost an hour ahead, won't we?

All right. So we'll take a 30 minute break and start the final closed sessions which make

the presentations, and then we'll take the votes on these laboratories. Okay.

MS. WALSH: In 30 minutes we will begin our closed session. This closed session is closed to the public. We are asking the public to leave the room at this time and take all of their possessions. Any briefcases, suitcases, or personal belongings left in the room will be placed outside the door before we begin our closed session.

For the press, any media equipment that cannot be removed in the next 30 minutes must have the power turned off. When the closed session is over, you can come and remove any remaining equipment.

DR. MARKOVITZ: Our luggage can stay in here, I assume.

MS. WALSH: Yes.

CHAIRPERSON OVERTURF: Okay. We'll reconvene at 11 o'clock.

(Whereupon, at 10:32 a.m., the open session of the above-entitled meeting was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Vaccines and Related Biological Products Advisory Committee

Before: DHHS/FDA/CBER

Date: February 17, 2005

Place: Bethesda, Maryland

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.