FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

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RESEARCH REVIEW SUBCOMMITTEE

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OFFICE SITE VISIT
OFFICE OF VACCINES RESEARCH AND REVIEW

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OPEN SESSION

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FRIDAY, MAY 19, 2006

The open session convened at 8:00 a.m. in Salons A-D of the Hilton Washington, D.C. North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland, Walter Royal, III, Chairperson, presiding.

SUBCOMMITTEE MEMBERS PRESENT:

WALTER ROYAL, III, M.D.Chair
JOHN BOSLEGO, M.D.Temporary Voting Member
RAPHAEL DOLIN, M.D.Temporary Voting Member
HARRY GREENBERG, M.D.Temporary Voting Member
ERIK HEWLETT, M.D.Temporary Voting Member
RUTH KARRON, M.D.Member
PAMELA McINNES, D.D.S., Msc.(Dent) Temporary Voting Member
ALAN SHAW, Ph.D.Temporary Voting Member
CAROL TACKET, M.D.Temporary Voting Member
BONNIE WORD, M.D.Member

FDA PARTICIPANTS:

JESSE GOODMAN, M.D., M.P.H., Director, CBER
CHRISTINE WALSH, R.N., Executive Secretary
NORMAN BAYLOR, Ph.D., Director, OVRR/CBER
MICHAEL J. BRENNAN, Ph.D., Associate Director of Research, OVRR/CBER
DRUSILLA BURNS, Ph.D., DBPAP
KATHRYN CARBONE, M.D., Associate Director for Research, CBER
HANA GOLDING, Ph.D., Chief, Laboratory of Retroviruses
BRUCE MEADE, Ph.D., DBPAP
RICHARD WALKER, Ph.D., Director, Division of Bacterial, Parasitic and Allergenic Products, OVRR/CBER
JERRY P. WEIR, Ph.D., Director, Division of Viral Products, OVRR/CBER

C O N T E N T S

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

(8:05 a.m.)

CHAIRPERSON ROYAL: Good morning. I'm Dr. Walter Royal, and I'd like to welcome everyone to the office site visit for the Office of Vaccines Research and Review.

We'll start off our meeting with some comments by Christine Walsh.

MS. WALSH: Good morning. I'm Christine Walsh, the Executive Secretary for today's meeting of the Subcommittee of the Vaccines and Related Biological Products Advisory Committee.

I would like to welcome all of you to the Subcommittee meeting of the Advisory Committee.

Today's session will consist of presentations that are both open to the public and closed sessions.

I would like to request that everyone please check your cell phones and pagers to make sure they are off or in the silent mode.

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

The Food and Drug Administration is

convening today's meeting of the Subcommittee of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. Our members of the Subcommittee 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 Subcommittee'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 Subcommittee 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, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the agency's need for a particular individual services outweighs his or her potential financial conflict of

interest, Section 208, and when participation is necessary to afford essential expertise, Section 355.

Members of the Subcommittee as special government employees, including consultants appointed as temporary voting members. Subcommittee members have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their employer, spouse, or minor child related to the discussions of the intermural research programs in the Office of Vaccines Research and Review. These interests may include investments, consulting, expert witness, testimony, grants, contracts, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda is devoted to the review and discussion of the intramural research programs in the Office of Vaccines Research and Review. In accordance with 18 USC Section 208(b)(3), general matters waivers have been granted to the following participants:

Drs. John Boslego, Dr. Raphael Dolin, Dr. Harry Greenberg, Dr. Ruth Karron, Dr. Walter Royal, Dr. Alan Shaw, and Dr. Carol Tacket.

A copy of the written waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12-A30 of the Parklawn Building.

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

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

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

CHAIRPERSON ROYAL: Thank you very much.

At this time I would like to welcome the members of the Committee. I would like to go through introductions of committee members, starting with myself.

First of all, let me just say that the site visiting Committee members are on my left, and FDA participants are on my right.

My name is Walter Royal, III. I'm an Associate Professor of Neurology at the University of Maryland School of Medicine in Baltimore.

I would like to start with other introductions beginning with Dr. Karron on the end.

DR. KARRON: Ruth Karron, Johns Hopkins University, Baltimore.

DR. HEWLETT: Eric Hewlett, University of Virginia in Charlottesville.

DR. WORD: Bonnie Word, Baylor College of Medicine, Texas Children's Hospital.

DR. DOLIN: Ray Dolin, Harvard Medical School, Boston, Massachusetts.

DR. BOSLEGO: John Boslego, Director of Vaccine Development, PATH.

DR. TACKET: Carol Tacket, the University of Maryland, School of Medicine in Baltimore.

DR. McINNES: Pamela McInnes, National Institutes of Health.

DR. SHAW: Alan Shaw, Vaccinate Corporation.

DR. GREENBERG: Harry Greenberg, Stanford University, Stanford, California.

DR. GOODMAN: Excuse me. And I'm eating a muffin and phone is ringing.

(Laughter.)

DR. GOODMAN: Jesse Goodman, CBER right here. Thank you.

DR. CARBONE: Kathy Carbone, CBER, FDA.

DR. BAYLOR: Norman Baylor, Office of Vaccine, CBER, FDA.

DR. BRENNAN: I'm Mike Brennan, Associate Director of Research and Office of Vaccines.

DR. WEIR: Jerry Weir, the Director of the Division of Viral Products at OVRR.

DR. WALKER: Dick Walker, the Director of the Division of Bacterial Parasitic and Allergenic Products at OVRR.

CHAIRPERSON ROYAL: Thank you very much.

At this time I'd like to introduce Dr. Jesse Goodman, who will begin the meeting with a presentation.

DR. GOODMAN: Well, you know, I want to thank Dr. Royal and the Committee and all of the extra people who have come to bring their expertise and give

us input, and I would also like to thank OVRR who has have been very busy, but who have been very willing to work together to prepare to present their program to you for your review and input. I will sort of give an overview of what we're hoping to get your input about, and then you have several other presentations.

I would like to just say that you should understand this in the spirit that it's intended, which is -- and in my view of science which I think will come across in some of this little introduction here, but I think that with rather strikingly hugh responsibilities, many of which are in, you know, very tight time frames and on complex issues, that the Office of Vaccines has done an excellent job, and I think that the need of strong underlying science and expertise to be part of that and supported in many areas is critical. And I'm very supportive of that.

Obviously that, too, we do, you know, in a very busy and also resource constrained environment, and I think that the scientists within the center -- and I always view science very broadly, and I'll mention this again, is not just being laboratory science but being population sciences and clinical science, et cetera; that that approach is just

critical and key, and that the performance there has been integral to our success.

So with that said, what we are looking for here is that the tradition within FDA and the center to the extent that there has been review and input about scientific research has been about individual programs, individuals, and what we are trying to get your help with and trying to put in place in this center, which I think is a bit of a seachange, is a more strategic approach, and some of this is dictated by a resource situation, but I think even actually probably if we even had lots of resources it would be even more important in some ways.

So where are things going in the next five to ten years? Are we adequately prepared? What should we be doing? What should we be focusing on with what we are doing? What can we do better? How can we do it better, et cetera?

So that is sort of the kind of input we want, and in that sense, outside input is very, very important because you have different perspectives, and we have worked with many of you or the types of institutions that you represent in achieving what we have been able to achieve, and we want to do that in

the future, too.

So this is just a little bit of framework. I always like to, you know, show our vision for the center because I think this is very critical in driving the science, and it seems simple, but it is not simple. So we see ourselves as being innovators in using innovative technology and as really having a public health mission and contribution. Our products are very unique even in FDA with respect to that contribution.

Our basic thing we want to do is protect and improve public and individual health in the U.S., and we have added to our mission the statement "and where feasible globally," because we see particularly in our areas like infectious diseases that we live in a global community, and we also see that industry is now global, and we think it is very important to have this vision and share this with our constituencies and the American people.

The public looks on us to make sure the products are safe and effective, and your committee was doing an important piece of that yesterday, or the VERPAC was. We also seek to take it a step beyond that because we believe these products when they are

safe and effective really help people. We want to facilitate their efficient development and get patients to have access to these products. And that holds with new technologies, too.

And then as per this discussion of science today, really our quality is critical in doing that, and that is one of the biggest challenges the government as a whole faces and FDA in particular faces. How do we maintain our expertise in quality with all of the challenges that we have?

Okay. So you're also talking, when you're talking at the center level, which we have to deal with, at the very least we're talking about a broad spectrum of important products of which vaccines is a very important component.

But if you think about blood and blood components and derivatives, people who do health care realize how important that is. We're talking, you know, something like 30 million transfusions a year and really CBER has this key role in all of that.

And if you ever thought vaccines was a stepchild of pharmaceuticals, think about blood. So we have real challenges there.

Allergenics similarly, and then we have

this wonderful whole area of what I like to think of as 21st Century medicine and cell and gene therapies, tissue engineering. Many of these products which go beyond a pharmaceutical model and offer the possibility to actually repair defects at the cellular or genetic level.

The tissues where we have recently increased our regulatory scope are currently without dedicated funding to do that. Similarly to blood, there are about one and a half million tissue transplants a year in the United States, and there are some real challenges in that field.

On the other, hand many people are really helped by these products. Very important and then a lot of related things.

What are some of our current big issues and priorities for the center? Many of these come right into the lap of the Office of Vaccines, but also our other offices. So certainly pandemic influenza is right now probably number one on our front burner of the stove, and it's intricately tied to annual influenza, and we've tried to make that point throughout.

This is one area where you should be aware

that in a general scope of constraining resources, ever constraining resources, we did get at the Secretary and President's request a supplemental appropriation of $16 million in 2006 to support our pandemic influenza activities.

And this is not just for the Office of Vaccines necessarily, but it supports a number of -- the majority of it is going there -- it supports a number of activities, review, manufacturing oversight and review, product quality and testing, et cetera. And we are just beginning to implement that increase, and I think it will be we are trying to do that in a way that strengthens our infrastructure overall and is a model for really targeting it at what are the problems that are very FDA mission related.

So we're going to do that in the scientific research aspect of that. We're going to do it in the review inspections, the safety and post marketing aspects, too.

Other emerging infectious diseases and counterterrorism remain a huge priority, and of course, the other things you see here are more generic, but I'll just mention a couple of priorities within them.

Product safety obviously for the FDA as a whole is a big issue, and then think of where we are in CBER. We have products such as vaccines that are expected to be nearly absolutely safe. So the challenges there are tremendous and are very safe. So the challenges are tremendous and some of the issues and how you use epidemiologic and population sciences are huge.

We, as I said, want to bring safe and effective products to patients, and a whole other area that has largely been overlooked that is encompassed in the agency's what has been called the GMPs for the 21st Century is the whole manufacturing end. So GMPs being good manufacturing practices.

And again, I think this is an area both where the FDA and the scientific community has not always invested much, and we want to look much more, and it is certainly not an area where typically academic or NIH science gets very involved, and it is an area where our CBER scientists and people in Vaccines have made contributions.

So I think there is an area there, and flu vaccine is a perfect example where we are using many technologies in product evaluation and testing and

even in manufacturing and process control that probably there are opportunities to in some ways improve speed, et cetera.

Along those lines, for example, we have started with our scientists and our compliance people are starting to have regular meetings with industry about vaccine manufacturing quality issues, and I think in the past the approach has simply been to go out, inspect, deal with issues or problems, and what we're trying to do is say, well, what are the recurring problems. How can we prevent them? How can we work together?

Okay. I think you have all heard about the FDA[s critical path initiative. This is sort of the lens through which we have to see what we do with our research and our resources. Again, this has largely been unfunded initiative, but the idea at an agency level is to do something very similar to what we've been trying to do at the center level, which is to focus the research on what is it that FDA is uniquely positioned to do and deal with opportunities to improve the product development process or product quality.

I think this is an opportunity, this

initiative, to promote and preserve a science based FDA, something that as I said I'm very supportive of. So to the extent that we can explain and articulate the mission of FDA science and have it focused on things where we make unique contributions, I think that can be very helpful in supporting it and in having it be as productive as possible.

So we have been embracing this and seeking input from the outside, and this is part of it. We had a large public meeting last October 2004, and we are having a series of site visits with our Advisory Committees with special members to get basically a first step in input into this process.

I think I'm preaching to the converted, I hope, but what are some of the unique roles of FDA science, and it is important for us to keep this in mind because there certainly can be overlap with what our colleges in academia or NH do, but there are some very unique things and there's a unique orientation.

And I think one of the things that we can't do is be duplicative. We want to be focused on things that are really related to our mission and are likely to contribute to our mission.

So some of the things involved in this is

that our people -- and this has been the model in CBER -- that our scientists are involved in the review process, and that creates some challenges that reminds me of what I did in academia. You know, I worked in a lab and also took care of patients.

Well, I think that gave me unique ability to ask and answer certain questions, but it is certainly a challenge. It is kind of like having two jobs at once, but our people see the successes and failures and missed opportunities in a way that one person in industry or somebody in the academic community won't see. We see it across multiple products.

We provide guidance and policy that affects industry and innovators in academia tremendously, and to the extent that the guidance and policy we can provide can be based on sound science, it's going to be better and get the job done better, and that's very important.

And also making decisions about studies, you know, do you allow an IND to go forward? What do you worry about about the product? If these are informed by people who understand the science of the product, these are going to be better decisions, and

as I said, these are unique responsibilities.

I also think there are opportunities. We have some scientists who come to FDA from a traditional background and get immersed in some of these kinds of issues and just really get turned on and love it and do very important things. So there is a model there that can really work, but the work load can be challenging.

So what have we done to try to sort of foment a movement from what I would describe as relevance doing research which is relevant to moving towards a strategic approach to relevant research, and we set up a research working group of high level people from within the centers and all of the offices. They spent a lot of time thinking about some of these issues. We had a retreat where we talked about the priorities and agreement was reached on what I would describe as guiding principles for our offices in the centers, a transformation into creating a research leadership council for the center that would coordinate across the center and some priorities for implementing these principles.

And Kathy Carbone will talk a little bit more about what is being done now to implement, but

just to show you -- and, again, this may sound sort of in the American as apple pie vein, but it's not that simple and it does, I think, guide and manage our work.

So the principles people agreed on were that the research program would be highly collaborative and include laboratory epidemiologic, statistical and clinical sciences, and by "include" I also mean where appropriate, integrate.

For example, now on the group's thinking about what should be our research priorities, we include full-time reviewers in that process. Its scope will encompass the scientific basis of product innovation, preclinical and clinical studies, manufacturing, again, as I mentioned, an often overlooked opportunity, regulatory submissions, inspections, post marketing surveillance, and the guidance process.

So let's get science input into those processes and let's get the input of those fields and challenges into how we direct and choose our scientific work. And of course we want it to be high quality, efficient, and directly managed and outcome oriented to address product development challenges and

safety, effectiveness, and quality.

So the goal of what we're asking your input about, and it's not simple. We're sort of looking for input and ideas to take forward in this implementation process. We want to do this as a periodic and recurring approach, you know, to sort of say, "Well, here's what we're doing to get feedback," to adjust what we're doing to get feedback, again, and that's part of what Kathy will say. That's part of the charge to this research leadership group, is to set processes in place to make this happen in the future, not on an ad hoc basis, but on a systems kind of basis.

But what we're going to want to do now and then recurrently is assess the focus, strengths and weaknesses of our research programs to assess our preparedness, not just for now but for the future is another huge challenge I think in the federal work force, if that many, many people are nearing ages where they can leave the government, and we really want to think about the future even when we have a very challenging past and could barely get through our work each day. We don't want to forget about the future, and we want to make recommendations help us

further the research that will really be key to our mission.

Important things also both that we're trying to do with you today but that we need to do with our various communities and constituencies in general are to increase the visibility and transparency of all of this effort. We want to communicate how the program is integrated into and with the regulatory process. We want to show the contributions to product development and quality and availability and, again, get your input. What should be the priorities? What should be the focus? Are there opportunities given the incredible breadth?

I mean, essentially at FDA you could be relevant to work on anything, okay, virtually anything, but where should be our focus? Are there things that we at this point, given how things have changed in the last five or ten years, where we should redirect some of our efforts, are there good opportunities for leveraging and new collaborations?

And I will say we haven't been sitting still, and the Office of Vaccines has been very aggressive in doing this. We've had wonderful relationships with NIAID, for example, you will

probably hear about, but a perfect example, I think, is work on cell substrates for vaccine production and testing and quality of those substrates, work that our people and inside and work on products are very important to and work that NIH is very willing to support because it helps further their goals of getting these new products and technologies out there, and that's an example of a great collaboration.

And again, our people are really critical, and you know, how do we get people who are unique, you know, who are high quality, excellent scientifically, but can resonate to this kind of mission. So input about that is appreciated.

So in closing I would say, and I never forget this. I have a different slide that's more basic about this, but you know, basically every year hundreds of millions of vaccines are given to people. Thirty-plus million people get blood transfusions. I mentioned a million and a half people getting tissues. This is a hugely important mission, and it is not a bureaucratic mission. It is a mission that is about science and public health, and we really want to support that.

And so, again, we really want your input.

I do have to apologize. As part of our pandemic things I have to run off and go get on a video conference with Germany, but we have got great people here, and I will read your report.

And also I would say to members of the visiting group, you know, we really do want your ideas, especially your positive ones, and I'm also open personally to phone calls, E-mails any time, and I just thank you very much.

I'm happy to take a question or two if anybody -- yes, Harry.

DR. GREENBERG: Could you just give us a little idea of once this report is written what's going to happen? I'm getting old, and I actually remember old reports.

DR. GOODMAN: Okay. Well, let's do it this way. Keep it short. Okay. So we're not looking for an exhaustive analysis of everything, but for good ideas, general feedback.

What we will do with this is we've had -- the two other product offices have had these reviews done, and we have read those reports. So that's the first step. We have at least read them.

We are going to ask this Research

Leadership Council and the Associate Directors of Research for each office, okay -- so each officer like Mike Brennan in Vaccines -- to look at these and use these and tell us what the response is to each of these suggestions that are made as they -- part of the mission of this Research Leadership Council and of the Associate Director for Research within the next several months is an implementation plan. So I want to know did we -- this is a very important piece of input then in that priority setting process, in that management process, in that long-term vision process.

So I'm going to really ask people like Norman and Mike Brennan to take this advice and tell me what they're going to do with it. Where our resources don't make it possible at least as we look for resources, it will help us prioritize how we do that.

So my view is I think there are much bigger, higher level issues, too. You know, there is a huge issue out there. It's like the 800 pound gorilla, which is -- I mean it's not even about research at FDA. It's about FDA in general. How does the public view FDA in general? How is the public going to support this enterprise?

And I think that particularly comes home with respect to science because for many people that's a hard connection to make. And I think the FDA leadership, myself included, are aware of that, and we want to try to move on those bigger issues, and some of those are being addressed.

You know, FDA does have a science. It's, I guess, called the Science Board that actually. Ken Schein, for those of who you know, Ken is now directing; from the ID microbiology point of view, Gail Cassell is also on, and I think getting them involved also in the larger big picture issues of what does it take and how shall FDA be a science based agency is something that we're trying to do also.

But it's a big challenge both in terms of understanding FDA and in terms of the overall federal resource picture right now.

Yes?

DR. GREENBERG: I realize the focus is on research in this particular session, but in my participation in lab reviews in the past, the panels have heard about the regulatory side, but have focused on the research there also.

I agree with you about the importance of

integration of the two and having the two being related to one another. I wonder what processes there are for review and evaluation of the regulatory activities of the people that are doing both.

You mentioned clinical and administrative or research that you've done in the past.

DR. GOODMAN: Yes, yes. Norman will mention this a little and so will Kathy, but it's an excellent question, and again, it's one I have history with in terms of, again, having been in academic medicine environment. It's very easy to look at somebody who is a full-time scientist and do an assessment. It's generally easy to look at somebody who is a full-time clinician, but people who are doing both, it can become quite challenging, and I think we have that challenge.

It is right now begin done in different ways in different parts of our center. For example, the Office of Cell and Gene Therapies has a rather sophisticated way of looking at work load of people and what they accomplish in the regulatory end as part of the assessment of them as an overall member of the group.

Norman can talk a little bit about how

they're doing that, but one of the charges to this leadership group is to try to get a consistent approach to this across the center so that the managers have objective information with which to make adjustments in workload, et cetera, et cetera.

So if you're talking from that point of view and to look at the quality. One of the things that I have said in the last three years when I have been center director, and I said this to Kathy and I hope she is implementing it; I mean that's what I hear, but is that it's not just to me that a laboratory scientist does some review work. It's also that that has to be high quality, done in a timely manner, et cetera.

And that produces challenges, you know. It's a challenging kind of position, but you know, the American people's biggest expectation of what we do is that we do high quality review, and that we make sure products are safe and effective, and I think, you know, that always has to be the first priority, to have that be at the highest level of quality.

And so that is something we're taking seriously, and again, we're trying to develop a more consistent approach, quantitative approach across the

center, and we would welcome, you know, your thoughts about that.

I wouldn't restrict your thinking to just what happens in a laboratory or in a statistical analysis, but to how we make this very challenging interface work. We don't want it to be so burdensome that people cannot function scientifically in our environment. We want to get the right kinds of balances.

I'm not convinced that it's exactly the same for every single person.

DR. GREENBERG: Do the proprietary issues preclude their being external people involved in that review process?

DR. GOODMAN: Of the regulatory work, you mean? I'd have to think about that, but I don't think necessarily, but I think in some ways when you get down to this really granular level of an individual person and their performance, in some ways then we're talking about what a good manager or supervisor should do, and I'd hesitate, you know, to expand that to the external world.

I think from the external world we look for feedback about what our people have done, and we

want that, and we look for principles. You know, do you agree with what we're trying to do here?

Any other questions? Yeah.

CHAIRPERSON ROYAL: As we make our recommendations, should we try to keep in mind certain time lines that might be required for them to be implemented? Certainly that's obviously something that CBER would be addressing, but you can imagine that our list of recommendations could go on to a certain extent.

DR. GOODMAN: Yes. Well, I see this as a continuing process, but I guess what would help in terms of your recommendations because often people make a lot of recommendations, is your sense of what's most important. If you had to put effort into changing one thing or supporting one thing, you know, what would be most important?

The time frames are reasonable. The time frames that fit with our processes is that I'd say within the next year we're really going to implement this management process and apply it to sort of our annual how do we resource our different projects. How do we choose among things when our resources are limited?

So I think we will use some of this input to either support what we're thinking of doing or perhaps alter it in certain ways within the next year in this process.

If there are things that we would love to do, like if somebody said to me, well, you ought to have a program in nanotechnology, well, I agree and would love to do that, but there are certain things where there may be things that we can't do under the current circumstances because of constraints, but we might say, okay, we're hearing from people who are very knowledgeable. Understand what we do; understand what the needs are out there who are saying this is important.

So in our process of planning and weighing various priorities, we're going to put that in there. Yeah, that's not a great answer, but you know, I think what I'm saying is we'll use your suggestions, both short term in what we're doing and longer term in trying to have a vision.

And as I said, Kathy will mention one of the things we've asked the leadership group to do is put together consistent methods -- and this is a first, too. I think we've always gotten input, and

we've gotten this input as was mentioned about individual investigator, but we do plan to have more transparency and get more consistent periodic input about the program as a whole. So I don't think any of this is static. We need to revisit.

You know, who would have thought we needed work in West Nile Virus, you know, five years ago? But we were very fortunate actually. This is one of the things about having a reasonable scientific infrastructure. We were very fortunate to have people both in vaccines and blood who could help us respond to that crisis, and in fact, take a leadership role.

Okay. Well, again, thanks very much, and I really would rather be here than running around like an H5N1 chicken with its head cut off.

(Laughter.)

DR. GOODMAN: Thank you.

CHAIRPERSON ROYAL: Thank you very much, Dr. Goodman, and of course, Dr. Goodman is the Director for CBER.

I'd like to introduce Dr. Kathy Carbone, who is the Associate Director for Research for CBER.

DR. CARBONE: Thank you, everybody who's coming to give us their expert opinions. We greatly

appreciate the time and effort you've made to come and help us.

And I hope to be able to expand on some of the questions that were asked and give some details about what we're currently doing to address those needs, as well as what we have planned.

You have this in your book because nobody can read this, but this is just to reinforce for anybody who is not very familiar with the CBER organizational structure that there are three offices, actually four, three offices that are involved in bench research, where another office does research of bioepidemiology, biostatistics and epidemiology.

But Office of Blood, Office of Vaccines, and Office of Cell Tissue and Gene Therapies have bench research programs. We've already reviewed Office of Blood and OCTGT, and this will be our third and final review.

And just to address a little bit the question of what we're going to do with this information is now that we have all three offices complete, the plan is to have the Associate Directors for Research in each office get together, review the coordinated responses because we certainly want to

look for common themes that occur among them, and we'll review this up the chain presenting it to the office directors as a summary opinion and review it down the chain, presenting it to the staff and then use this in the Research Leadership Council to help develop a strategic plan for action.

So I want to address a little bit more about the critical path because I am very fond of it because it gives my life meaning. It gives me a way to explain why we do research in a way that is approved by the FDA. We are also interested in our FDA approval in that regard. And it's very hard for people to understand what it is we do.

I had a big discussion about a matrix recently and research for a disease that doesn't have any particular therapy, and I made mention that in terms of prioritizing research. We needed to think about those areas of the research that would make drugs possible, this thing, that thing, this thing, and that thing. That's how to prioritize.

And somebody said, "Oh, right, right. Molecular targets, we need to find molecular" -- I said, "Well, that really wasn't what I was talking about. I was talking about the evaluation process."

But since nobody but the FDA and industry is very familiar with the evaluation process, the science of the evaluation process has been fairly neglected, and that critical path initiative gives us the opportunity to talk about that a little bit and try and get some messaging out.

So when the original critical path document came out, Dr. Woodcock quoted a figure of $800 million to develop a drug. It turns out she probably undershot because in another Science article, their estimate was 1.9 billion, and that is a tremendous amount of investment.

I recently heard of a program through another federal agency where they had a project to develop innovative drugs, and they were going to send grant money out, et cetera, et cetera, and I said, "How much do you have to spend?"

And they said, "Two billion."

So I said, "Okay. That will buy one drug."

I think most of the world is really not aware of that cost, and of course, this delays availability of important public health products that we deal with, and the question is: how can CBER

assist in this process?

The article in Science went on to talk about management of the scientific process to sort of the academic investigative, discovery investigator. The word "management" is counter to the actual act of innovation and creativity and science, but using intuition to support important public health in managing extraordinary amounts of resources for a car to produce drugs just simply is not satisfactory.

So models need to be developed whereby the creativity and innovation can occur, and yet the management to a target is there so that we actually end up with something at the end of the day. That essentially is in a nutshell the critical path science.

Most of you know how this works. There has been a tremendous investment in basic research and drug design, and as a result, there are many drugs sort of waiting with the motors idling that need to get through the process. This is particularly true for our category of drugs that are very innovative, such as cells and gene therapies. There aren't regulatory pathways, and the science is so innovative we certainly can't use 20th Century -- in some cases

we still use 18th Century, 19th Century medicine -- evaluative tools to evaluate products. That just can't happen. The tools need to catch up with the products.

And in our products, in particular, getting involved very early in design and preclinical testing is absolutely mandatory. So we don't want drugs to fail here. We'd love it if we could figure out which ones should fail there, and then supporting resources with the products that will end up being safe and effective and innovative will be the hoped outcome.

I like this figure from the document as well, and I continue to show it because so often science and research is shown as some little blip on the side of the regulatory process.

We answer questions as much as possible based on the science, but every day, as everybody knows, we identify and have to produce answers where the science is grossly inadequate, and we do our best job and use scientific judgment, but it would be much better to get as much information as possible while not holding up and, in fact, accelerating the process.

And so the science comes out, in our case,

comes out of the application review and discussions with sponsors of whole categories of products. We identify gaps. The research we hope to have done either in academia, government, industry, FDA, anywhere. We hope some of this effort promotes and stimulates others to do this kind of research to come up with a scientific solution which, in our case needs to be carefully vetted. Unlike a lot of exciting publications and exciting and advanced scientific journals that prove to be false or inaccurate six months to six years later, we have to be right, as right as possible with our science.

And so careful vetting, careful peer review is critical, and that committee, many of which you serve on, it's a critical part of that issue.

And then the guidance based on science makes more sense because what we're looking for is predictability, and so this is the role of science in the process.

So why is CBER and why should FDA be involved? After all, all we need to do is read papers and say up or down.

Well, what we see and the knowledge we see in the evaluative science is unique. We see problems

across whole categories of drugs. We see small things, the horseshoe nail of research essentially, the horseshoe nail of product development that without that small answer the product either doesn't go forward or a product goes forward which in retrospect was not the best product it could have been.

So we have developed here a concept to try and explain internally as well as externally, you know, science, you know, why FDA and research. Well, in part it's one of the few places, the other one being industry where an expert in a product, vaccine, a blood product, is also an expert in a scientific area, retrovirology. So we have retrovirologists that know about vectors. We have retrovirologists that know about vaccines, and we have retrovirologists that know about blood contamination, and that's a unique viewpoint that isn't seen very often outside of a proprietary setting.

And through guidance documents based on science we hoped to provide a clear path, and a secret to product development, of course, is predictability, being able to predict preclinically which products should go into clinical trials safely and will be safe and effective, being able to predict what the product

looks like to predict consistency of the product.

And the final thing is sort of being the disinterested. We spent a lot of time with conflict of interest issues and avoiding them and steering clear of them here at the FDA, and that gives us a role as the disinterested party that can serve as coordinator among several parties without any particular interest except the public health.

Multi-tasking, this was mentioned a little bit by Jesse, and that is I came from academia, and in fact, this very much to me resembles that academic program in the sense that our investigators, research regulators are pulled in many different directions, and they also need to scrounge about for extramural funding in order to survive. It's not too different.

The target is about 50-50 research regulation, but it's very clear that when a product comes around and that BLA hits the door, the research projects stop.

Similarly, if there is an emergency, somebody who is working on A will redirect to B because of needs, but they do the gamut. The review INDs and BLAs, develop guidances, meet with sponsors and advisory committees, participate in inspections,

adverse drug reactions, risk assessment and also perform research.

This is a very different model in case you don't know from other centers. Most of the other FDA centers, the researchers serve purely as consultants and aren't part of the regulatory process, although that seems to be drifting towards our model a little bit.

So how can this be done, the critical path? I think a lot of people's visions of the critical path is different, and Jesse and I have basically a tripartite view of the critical path and how to get it accomplished.

The first is by strengthening CBER intermural research programs by CBER and other FDA centers working collaboratively with other scientists, and frankly, by generating interest and knowledge about this type of research in the extramural community and encouraging them to work as well, and all of this information contributes to our regulatory process.

So I will go through this as a little bit of a culture change I've tried to push a little bit because when trying to understand the relative role,

say, of the NIH and the FDA, the response is, well, okay, FDA shouldn't do research at all. Once we get past that hurdle it becomes, "Oh, I see. NIH is basic. You do applied."

And in fact, I have tried to explain in this slide it's not a basic versus applied. It's research activity that's applicable. So the direct line, the dots have got to be connected between the research project and the outcome to support regulation, but the type of science doesn't matter. It's foolish in my opinion to limit scientists and the type of science.

For example, very good scientists, a specialist in re-docs, adverse events from hemoglobin based oxygen carriers, paired up with a mass protein chemist and use mass spectroscopy to do beautiful high quality, edge of the wedge characterization of hemoglobin based oxygen carriers, which has now essentially become the industry standard of revaluation of these products.

Methods validations for TSE, something very simple and applied, but something critical. If we don't learn how to inactivate pathogens from complex biologics, we are forced to discard otherwise

valuable material.

An example also from this particular office, and I'm sure they will elaborate on that, is investigators who developed a new biochemical process for glycoprotein vaccine conjugation. Very basic biochemistry, but it was such a good leap of improvement in terms of developing this it became immediately applied in studies in the community developing world, but it was basic biochemistry.

We now collect as part of the question of how we integrate and understand the relationship, direct relationship between regulation and research is in their annual research reporting we now collect the biological licensing applications and investigation drug applications must be listed that apply to this particular research project. So that's one level of information that we now get which is new.

And doing an assessment of the research projects based on the annual web based, about 40 percent of our work is in product safety, product quality and efficacy split, 50 percent or 25 percent each, and other is ten percent.

And I think this is interesting and important, as mentioned by Dr. Goodman, that the

safety bar for our products is often quite high, and I think even in the relatively lesser managed state, which we are changing, that was recognized by the investigations and appropriately focused on by the investigators.

So what are specifically the big picture, which is sort of my job here? And that is to create efficient, high quality, regulatory pathways where there are none, as I mentioned previously, applying 21st Century science to modernize pathways that may have been 30 or 40 years old that need to be brought up to speed.

The outcomes identifying and resolving specific high priority scientific challenges and product evaluation, and as you know, research is a Titanic. We have to predict five years down the road when there's a problem that's going to arise so that the product is not delayed or showed at the end of development, but enhanced and facilitated right from the beginning.

Data quality, as I mentioned, is a very important concern for us. Increasing CBER's impact and visibility because sa we increase our availability, this is not simply a "look at us; aren't

we great?" The more people who understand about this kind of research, the more people we can engage in doing this kind of research and the more people we can get to help us do our job better.

Funding these efforts is critical. As you'll hear from the office, the substantial portion, the majority of our consumables and soft money post-docs come from outside granting opportunities, and that's just a matter of life. You'll hear more about that today.

And then part of my job is providing core research reports. As many of you know, we have an excellent core facility which now has DNA, protein, RNA, and now even proteomics opportunities, and we do this to sort of enhance the investigator's functionality so that they now have options to support their research. In fact, to the Corps Director's credit, NIH utilizes our services in many institutes.

CBER research, managing regulatory challenges into successes. What we have incorporated in our management which are new. There is a formal process for internal expert evaluation of proposed research plans. So this is done by the offices. The investigators are asked to write what is your one year

and five year goals for your research project. This is evaluated internally by the office, the Director for Research in the office, as well as an external review, which I'll talk about in a minute.

There's internal/external evaluations of past research achievements. Obviously we're highly outcomes driven, and so these are reported every year and evaluated, and keeping in mind it's a little fuzzier than academia publications and publish or perish. Ours go way beyond that, but other kinds of documents that we count regulatory policies and guidances invited talks, research, Q&A and talks for example.

Internal management reviews are done on a yearly cycle on every research project for that annual web-based reporting and then the external site visits which as you know, as mentioned occurred in a laboratory regulatory researcher/reviewer level, but now we have the office site visits.

One of the things that has happened since I came in is we now, although we do review the individual investigators, they are now always reviewed as a laboratory administrative unit, and that did not happen in the past, and the reason we now do that is

that we want the site visit committee to be able to comment at least to the laboratory level on the essential portfolio of the research projects and the laboratory administration. Does this laboratory make sense? Are they covering? And to do that, they need to see all of the investigators in the laboratory.

What we've done in terms of better linkage of regulatory work load and the researchers is now they are no longer giving a paragraph that says, "I am the reviewer for X virus." What they're actually required to present to the committee is numbers of BLAs and INDs, guidances, recent cleansed, without proprietary information, simply numbers, issues that may have arisen, advisory committee meetings they needed to run, and it is done in a very quantitative fashion, and in fact, it made my heart feel good when a single advisory committee chair who had done two different laboratories out of the starting gate made the comment, you know, "It seems to me this laboratory does more regulatory work than that laboratory."

So he was able to make some kind of assessment, although that's not the job of the review group to review the research in this setting. It's important that they know what the work load is and how

the investigator is performing. It gives them an idea of the relative productivity on the research side.

However, on the internal committee where we can talk about specific documents, there's a promotions and conversions evaluation committee. We have changed that to now have a dual track review. There was formerly a research review with a comment by a regulatory scientist of the individual's regulatory contributions, okay, not okay, good, bad.

We now have a duplicate review. The rigor of the research review is duplicated now by a review on the regulatory work load, which includes a primary and secondary reviewer from the research side, as well as the regulatory side. So we do a completely independent evaluation of that candidate.

Now, we had to come up with this ourselves and we did it with the approval of the FDA because there is no mechanism currently for doing this in the government. People are viewed as single units of expertise.

So what we have essentially is duplicated. So now every review the research regulator gets a complete review and evaluation of the quality and quantity of their regulatory work, as well as a

separate review of their research and that's used to evaluate the person, and that is new, and I have to give a lot of credit and thanks for a regulatory scientist, compatriots who are willing to invest in the time to do this on that committee, and we plan on continuing to enhance that.

Research Leadership Council, as Jesse was saying is involved in and has been tasked with essentially taking these kinds of efforts, which are being instituted in sort of current processes and developing whole new processes. This is essentially grassroot efforts because there is representation of the research leadership and regulatory leadership from every office, and we have already an outline of a yearly process which we are drafting into an SOP form so that the offices can adapt it, and it does things like assess work load, assess productivity. How are priorities set?

It's very easy to say, "My priorities are X, Y, and Z," but as Dr. Goodman was saying, they change so frequently. A much more important way to think about it is how do I determine priorities.

One of the issues, for example, is doing a review of the regulatory work load, the scientific

expertise required for that regulatory workload, and looking at how our research profile and staffing matches the effort as part of it.

But I'm sure we'll come back at some point and present that at another site visit when that's finalized.

We have also developed a concept of virtual teens being a very thin and understaffed program. No person is an island in research. We now have developed a virtual team concept, which is going to go up on our eternal website as our research programs are now up on the external website, except for one office, which is working on theirs.

The virtual teams will gather together and say our retrovirology expertise across the whole center and form a cohesive group both for tapping into regulatory needs, but also for developing more a critical mass for research.

So I'll just end with some practical world examples of the things that we're interested in. Better biochemical characterization of complex products would be a great boon so that we would have better predictors of essentially what is the efficacy linked component of a complicated product and how

changes in the product may affect efficacy and safety.

The example I used for hemoglobin based oxygen carriers, essentially that has been done for that level, and it was a very, very excellent piece of work. We would obviously like to expand that to as many products as we can. As you heard, we had a large interest in cell substrates which are critical. Appropriate toxicology approaches for complex biological products, we now have the first national toxicology program effort to look at a toxicology model for gene vectors and oncogenesis, which is way outside the standard realm of toxicology of liver damage, heart damage, et cetera. This is something completely new, and we're collaborating with our NIH colleagues to get that done.

New assays. Sometimes this is a real horseshoe nail, and you'll hear some examples from vaccine where a simple, little assay made a huge difference in the ability of products to move forward.

And multi-pathogen and rapid detection methodologies, and as I said, something truly novel in activation methodologies. And of course, I don't mean to dismiss at all the importance of non-bench related research at CBER and there is other components of that

as well that are very contributory.

And I just wanted to thank you for your expertise and time and assure you we will read and listen and review your comments and those in Research Leadership Council will make sure that they get instituted as best we can, given our resources, et cetera.

And I think we're going to go to Dr. Baylor and then questions.

CHAIRPERSON ROYAL: Let me just say that Dr. Norman Baylor is at the podium. He is the Director of the Office of Vaccines Research and Review.

DR. BAYLOR: Good morning. I wanted to thank the Committee also for taking the time out to review our program.

I think what I'm going to try to do in the time allotted is provide an overview of the Office of Vaccines, and I think it's important to put some things in context for you to -- as you think about evaluating our program, I think you really need to understand how the office is organized, what the office is up against, and so putting that into context for you.

I start out with our mission statement. Our mission statement is very important, but simple. It's to protect and enhance the public health by assuring the availability of safe and effective vaccines, allogeneic extracts, and other related products.

How do we accomplish this mission and what's involved in activities in performing our mission? We review applications such as INDs, biologic license applications and amendments for vaccines and related products. We're also involved it's obvious from this site visit in conducting research related to the development, manufacture, and testing of vaccines and related products. We also are involved in developing policy and procedures governing the pre-market review and evaluation of vaccines and related products. We also evaluate and test vaccines and related products, both pre and post licensure. We evaluate and monitor clinical experience as far as adverse reactions and collaboration with our sister office, the Office of Biostatistics and Epidemiologists. We also participate in inspections of manufacturing facilities, and we do this in collaboration with the field, as well as our Office of

Compliance, and we have a very important presence in participating in national and international outreach, such as organizations of the World Health Organization and other national regulatory authorities throughout the world.

This is the Office of Vaccines, and I just show this slide to show I think I should emphasize here that the management team is relatively new in the Office of Vaccines. I've been in this position almost a year. This is an opportunity for us to restructure the entire office, and so we are trying to do that in a time when there are many changes in the agency as well as changes within the center.

Who are we? We're the largest office, product office in CBER. We have a staff of over 300 employees. These employees are divided between the immediate Office of Director -- that's my office -- and also three other divisions, and we also have product testing laboratories which are part of the OVRR Immediate Office of the Director.

We have an Applications Division, the Division of Vaccines and Related Products and Applications, which we like to refer to as DVRPA, and this organization is composed of non-laboratory based

regulatory review scientists, and also our clinical reviewers for the most part are in this division. We have two lab based divisions, Viral Products and Bacterial Products, and these two divisions are predominately staffed with laboratory based scientists.

This team, if you will, these three divisions are involved in at least on the review side and to some extent on the research side. It's a collaborative effort. It's a team. We pull the necessary human resources from these three divisions to carry out our mission.

I wanted to show this slide to show, to demonstrate our staffing over the years from 1999 to 2006. This slide is somewhat deceptive. We have seen that our overall full-time equivalents have increased from 1999 to 2006. We have approximately 262 -- at least that's our ceiling of full-time employees or FTEs, and the full-time employees for you non-government committee members, these are, quote, permanent staff.

And then we have a staff of close to 100 post-docs. These are not full-time equivalents. So that puts us over 300, and I think what can be

demonstrated from this slide also is that we maintain a training program so we can bring in scientists from around the world to receive training here, and scientists still want to come to the FDA, come to CBER for training because we provide a unique opportunity for these individuals.

What is the role of research in the Office of Vaccine? It supports a science based regulatory review and decision making. It allows expert review of regulatory submissions such as INDs and BLAs that I have mentioned.

It also allows us to address product related issues in the laboratory. So when there are issues with sponsors and manufacturers, we can address those issues. We are constantly working with the industry to resolve challenges and issues and the laboratories allow us to do that and have that ability.

Also, the research influences policy and guidance. I mean, when you're putting out policies and guidances to drive or to try to lead the industry and sponsors, it's important to have laboratory experts who can contribute to those guidances and those policies.

So that really make CBER and OVRR, in particular, unique because we can draw upon that expertise. The research is an essential component of the regulatory review process to assure the safety, purity, potency, and effectiveness of vaccines, but it needs to be open ended to provide the ability to respond to new areas.

We cannot be so narrow, as Dr. Carbone mentioned. We have to see the future, and we have to be able to respond to the future. So we have to have a program that will allow us to do that. So we can't have a very narrow program.

And the research program also serves to recruit and maintain highly qualified staff, not just for the laboratories, but also for our applications division.

The priorities, certain programs, it's obvious that there is a broad range of scientific disciplines, and it's key to have these scientific disciplines to allow us the flexibility to respond to emerging issues. These must be maintained for their importance to the general needs of the office.

The areas of priorities, the priority areas are established by the office leadership in

concert with the scientific staff. So, again, it's a cross-collaboration, if you will, between the staff and the leadership to decide on the priorities.

It's important to note that the needs of the regulatory process drives the research priorities. If no other message you get from here, it's that the regulatory process that really drives our research, and that's what makes us unique, and it requires a broad research expertise, as I've mentioned in vaccine related disciplines.

So we have to have a variety of disciplines, bacteriology, microbiology, molecular biology, clinical medicine to be able to meet our mission, and it allows the office to shift priorities when public health emergencies arise.

The research projects and their relative priority, of course they change over time. They change with new and evolving technologies, and so it's necessary for us to continually evaluate our research needs.

In the process of setting priorities, the ultimate decision of prioritization results from a reasoned evaluation of the following. We have priority setting by relevance. The nature of research

programs depends on their importance.

Now, one may ask: well, importance, it's a relative term, and sure, it's relative, but the importance is dictated by, again, the regulatory process. What are the emerging issues? What are the emerging public health issues? And we need to be able to draw upon that in order to set the priorities by relevance.

So the outcomes have implications for an extensive set of existing issues, product safety, characterization. These are issues that we have to face all the time, and by having the research program, we can address these.

Priority setting is also by uniqueness and feasibility. The uniqueness comes from the fact that the scientist in the Office of Vaccines are in a unique position because of the specialized knowledge they have and also the ability or the availability of reagents and the technical expertise. For example, looking at potency assays or developing serological assays.

Our scientists see things from everybody. So when there's a problem, we know there's a problem, and we can address those issues. We are in a unique

position to be able to address those issues because we do see all sides.

We also have to deal with special considerations. The research programs, and I keep harping on this, they must be able to rapidly respond to emergencies as they arise, and so that's where having a multitude of disciplines allows you to do that.

The high research priority areas, and Dr. Goodman mentioned this, Dr. Carbone as well, safety issues related to vaccines and related products, product characterization, identifying immunological mechanisms, the mechanisms of pathogenicity, and emerging issues. And these are broad areas, but again, the regulatory submissions that we are getting fit within these areas and allow us to respond by having research that can address any of these issues.

Our current research areas with increased attention, our counter-terrorism program, anthrax, smallpox, plague and others, the research laboratories are critical in the development of animal models for the animal rule, and I can talk about that later if you'd like, pandemic influenza is top of on our list. Use of new technologies for influenza, such as

adjuvant, cell cultures, what have you, development of new assays.

Cell substrate continues to be a current area with increased attention, and also in our allergenic group, the allergenic structure and function.

So in summary, but before I read this slide, I should say something about Dr. Carbone mentioned about -- commented about our resources, and one thing you should keep in context is that our research program, it's primarily externally funded, with the exception of salaries, and those salaries would be for the full time equivalent employees from that slide I showed you before.

But for supplies, the majority of our resources come from nonappropriated FDA funds, and these resources are applied for by our scientists for the most part on a competitive basis, and this is what really funds our research program.

I have to stand up here and give credit to the researchers at OVRR because they have done an excellent job. They have done more than an excellent job in bringing in these resources to continue the mission.

So in summary, our research program serves to recruit, retain, train highly qualified scientists who possessed the necessary knowledge, technical skills to conduct research and review that will facilitate the development of new and innovative vaccines and related products that are safe, effective, and will contribute to the health and well-being of the public.

Thank you.

And I guess we can take some questions.

CHAIRPERSON ROYAL: Okay. Thank you, Dr. Baylor.

Any questions for either Dr. Baylor or Dr. Carbone?

Dr. Karron.

DR. KARRON: I think this could be a question for either or both of you, and it's really following the take-home message that you mentioned, Norm, which is that the needs of the regulatory review process drive the research priorities, and I guess my question is is there a mechanism -- I know from individual lab reviews that people are reviewed for quantity of regulatory burden, but is there a mechanism in place to review timeliness and quality of

review not only as a mechanism for reviewing that individual, but perhaps for identifying gaps in the program that need to be filled by other individuals?

DR. BAYLOR: I'll start off. Yes, we do that internally. I mean, we do from the Office Director on down to the divisions, and the divisions will speak shortly, but we review the quality of the research as well as the regulatory component of all our employees. I mean, our employees, our non-lab based scientists are promoted. There's a peer review process that they have to go through, and the quality of their work is reviewed. The same for the research scientists. They go through a promotion and tenure committee, and the regulatory work is reviewed.

And I also look at a number of reviews and discuss with the Division Directors. It's more feedback, giving feedback to the employees as far as areas for needing improvement.

Cathy, do you want to?

DR. CARBONE: Did I hear you correctly that you're talking more about programmatically across the center?

DR. KARRON: Yes, I was.

DR. CARBONE: Yes. Well, one of the

things, and I don't want to hold anybody to this. this is a very draft form discussion, but this virtual team's expertise database that we have for the research regulators, we're in early discussions with the regulatory scientists, leadership and some of the offices, to fold in all scientists at the center, including the regulatory scientists, clinical review scientists, et cetera, so that that starts us off as a tool with what expertise we have, knowing what's doing the assessment with the Research Leadership Council. Again, this is for the research regulators, but it's always applicable to the full-time regulatory scientists if their leadership should adopt it, is to make the assessment of what expertise needs are there in the current and anticipated major areas and novel areas as Dr. Baylor said.

And that makes it easier to match up and review, and, in fact, when I handed these out to the ADR as sort of the first blast of the virtual expertise, it's very interesting because people said, "Oh, we have a fair amount of expertise in this, but you know, I don't see this on the list."

And immediately it was apparent to everybody. So I think start with where we are and

start matching that up with where we have to be. I think that tool will be very helpful.

CHAIRPERSON ROYAL: Dr. Dolin.

DR. DOLIN: I wanted to follow up on the point you made a moment ago about the research program being funded by sources outside the FDA, and I think Kathy made the same point and so does the report. So it's a two-part question.

What are the ground rules for access to such resources? And then what is being done to facilitate the ability of the investigators to access those sources?

DR. BAYLOR: Okay. You start.

DR. CARBONE: I'll start with the center level, and then Dr. Baylor will take over.

There are definitely ground rules, and conflict of interest is one of the biggest. The second one is federal basically law with moving money from federal agency to federal agency, and we have to comply with conflict of interest laws as well as these federal laws.

One of the things we've done to make that process more streamlined and visible and transparent to the leadership is in the last two years myself and

Dan Murphy who works with me, I've instituted what we call the research administration process, and what happens is before any external grant, external to the FDA -- we made the assumption that if the FDA is offering funds, that those funds are accessible to us -- but anything outside the FDA, including other government agencies, they need to give to their leadership and ultimately ending up to me. They fill out a form basically that talks about the topic of the research, what the mission relevance is, any potential conflicts are reviewed and evaluated and signed off, and the sources of the funds so that we can evaluate.

For example, Dan Murphy, one of his jobs is to look at the source of the funds, and if there's an unavoidable conflict, then the grant is denied. This is before grants even go outside our center.

Those that go outside the government then go to the Office of the Commissioner for review and approval based on that information, but before they even get to me, the Office Director and the leadership within the office must sign off. So this process is to have it all in one place essentially to deal with those kinds of issues.

In terms of facilitating it at the big

level, Dano and I wrote basically a white paper for the Office of the Commissioner outlining ways to get research funds into the FDA in a legal and appropriate manner. There currently is no good way to sort of if somebody said, "I have a lot of money and I'd like to set up some sort of program to do research on some major public health issue," it would be difficult to transfer those funds to the FDA.

There are small ways we can do it in a specific project. There's the CRADA cooperative research agreement you may be familiar with, which is a legislative process, and that all grants to through We have no FDA foundation, for example, like NIH.

And the good news is, of course, that is the decision of our leadership in the Office of the Commissioner. The good news is we have recently been contacted for more discussions on that. So at least they're reviewing this information that we've sort of put in one place.

Essentially we did some ground work to help them in getting some information gathering on how to do that, and then there is sort of an individual institute-to-institute bridging, NIH, for example, NIAID. I think Dr. Brennan can talk about some things

that he has done that are really outstanding, where we find isolated areas that we have expertise that are definite gaps in everybody's research program and then seek opportunities to get those supported.

Foundations in general are okay, disease oriented foundations in general. We have to, of course, review each one, but those are sort of the big level pictures.

DR. DOLIN: For the typical NIH sources --

DR. CARBONE: RO-1, extramural funding.

DR. DOLIN: -- I gather you're not eligible for RO-1s.

DR. CARBONE: We are not eligible to be principal investigators, but under special circumstances, we are allowed to be co-investigators without salary support.

In fact, I just met with the head of extramural NIH, the whole extramural NIH to talk about those specific conditions, and I think we were in good agreement that based on staying in alignment with NIH policy, as well as the legal guidelines, definitely those are options to us.

And we have firmed up, and I'm meeting with the Commissioner's office, in fact, in a week or

two to establish a clear policy internally that allows us to be considered for those sorts of options. Currently we have several type like that, but you know, it could be better.

DR. BAYLOR: And let me just comment on that. I mean, I think what Kathy described to you is, I think, that demonstrates the limitations we have on where we can receive outside funding. So, I mean, our investigators are having to compete for much of these funds. They could not compete for funds widely as, say, an academic could

I should say for the record, too, that our preference would be to have appropriated funds to do our research with.

CHAIRPERSON ROYAL: Dr. Tacket.

DR. TACKET: So what happens if one of your researcher/reviewers loses his or her external funding? Does that means there's a risk that an area of expertise that might be necessary for the overall mission might be lost over a period of time?

DR. BAYLOR: I'll put it simply when they lose it, it hurts, but I mean, we do have some appropriated funds. That's part of the shifting of priorities. I mean, if there's a priority issue, and

we have some areas which, as I mentioned in the example where there may be areas which are not highly funded that we have to sort of supplement with our appropriated funds.

We have some appropriated funds, but again, we would be somewhat limited, but we have to continue our mission. I mean, we have no choice. We have to. So we do the best we can with what we have.

CHAIRPERSON ROYAL: Dr. Hewlett, I think you had your hand up.

DR. HEWLETT: I'd like to back up a little bit. I appreciate your description of the process in establishing priorities and the relevance and uniqueness and all of those things, but I don't understand really how it's done. As those of you who have been in academic institutions know, what research somebody does is a cottage industry. They decide what they want to do. They get funding for it or they don't, and that's what enables the research process to occur.

It sounds like you're describing that in part, but also it sounds like you need to do something that is somewhat like industry in which people are assigned to cover a particular area of research, and

so can you explain to us exactly how this works? Do you tell people who to do? Do you recruit people on the basis of their area of expertise or how does it work?

DR. BAYLOR: Okay. You will near more of this from the Division Directors as well, but it's a mixture of both, and there's a lot of history in this. It's not quite a cottage industry and we do to some extent -- we may have to dictate certain projects, emerging areas or emergencies that come up, we may have to say that project that you're working on you'll have to stop to address this issue.

But what we want to try to do, what our goal is is to have -- I don't micro manage the research. I don't want and the divisions don't tell an individual, "This is what you're going to work on and that's it." I think we need the flexibility. We allow the flexibility to some extent.

Again, I go back to the discipline. We need those disciplines in order to carry out our regulatory mission, and so we need that. We that expertise.

We are not going to necessarily dictate down to exactly what the project is, but that

individual has the skill set to respond to issues that may be emerging that we may have to -- I'll give you an example. The cell substrate issues that we've had and adventitious agents. We have had to, and we've done quite well in that area, we have had to dictate certain projects not down to the individual project, but the overall to address certain issues that have arisen.

But I don't know if I'm being clear or not, because it's a very complicated process because, again, the research is driven by the regulatory, and that sets the priority. And so if an individual is working on a given project, again, I'll go back to the cell substrates, we're not going to dictate the very specific project that that individual is responsible for.

We also recruit based on the expertise. I mean, if we are weak in a certain area, we will recruit in that area to bring on that skill, or if I know a certain product is coming on, I mean, for instance, we have sort of been able to balance this with some of our bio-T efforts. We've had people who could make the shift. For example, our pertussis lab, they've been able to make that transition for the

anthrax.

Others we've had to recruit to bring on into that area or we may not have had individuals in that area. Another example is our influenza lab where we have an influenza lab. The influenza lab was relatively small. We know we have a huge effort now in pandemic influenza. So we're recruiting to bring on more experts in that area.

So what you're saying is you have people who are covering subject areas, but not answering specific questions. Is that --

DR. BAYLOR: I would say they are covering subject areas and they have the skills and knowledge to address specific questions, and that does arise where they will or may have to address specific questions.

Even in the review of applications, specific questions will come up, and we may address those in the laboratory. Another example is -- and I mentioned it on my slides -- like potency assays where we've had applications to come in and the manufacturers have had difficulties really coming up with very good potency assays. So we've collaborated. We've had people to collaborate with sponsors and

say, "All right. We'll work this out. We're going to work this out together."

So that is a specific project that they're working on.

CHAIRPERSON ROYAL: Dr. Greenberg.

DR. GREENBERG: I'd like to thank both of you for giving a good overview.

I have a question about the virtual network or sort of the matrix. The write-up was very lab specific, and I was wondering whether any materials for the Committee to understand these overarching themes that cross because that would help me specifically get a better idea of, well, for example, immune responses, how that spreads across to see where you are in sort of organizing in an interdisciplinary way.

The second question I have is, well, the NIH crash landing is affecting all of us in academia. I imagine it's going to affect you at the FDA since you are linked to extra FDA funding, and there are going to be many more people chasing the same funding you are.

What planning are you doing to maintain your small extra FDA funding base, which is going to

be under tremendous pressure in the next five years?

DR. CARBONE: Let me answer your first question. I can provide the Committee with some draft materials we have up on the Web. We started with the lab based information, but the nice part about this is the first half of the investigator's summary -- this is now on an external website because for the first time there really wasn't any information about our research program.

What I asked them all to do is for sort of public consumption write a short summary of their research and divide it up into public health issue, regulatory issue, how their research addresses that, and what their outcomes.

For the scientific audience, then we include the last four years of their publications. So this gives the outside word an opportunity to tap in. That's lab based, and we started there because that was already in existence.

What we have now is a draft document which will be going on the Web shortly after I get it commented on and finalized by the office ADRs. Of the six expertise teams and within that subarea of expertise with individual investigators, and those two

Web site will be linked. So you'll see these six investigators, retrovirology expertise. You can click on their names and find out specifically what they do.

So I can get you some draft Web pages, and also the Web sites in case with all of your time you want to click around, but at least it will be up there, but it's very, very at the preliminary stages.

The second thing, we're doing basically what everybody else does. I, frankly, believe some of the concerns we ran into about extramural and NIH and grants and how we can position ourselves, came up because of exactly this issue because the funding is very tight, and they are now taking very close looks at how things happen, and there were certain things that we need to be very specific about so that NIH is very clear on how we meet the policy so they can fund us.

I believe some of that was increased attention. The good news is that, for example, this office has just negotiated a very important additional grant from NIH or fund from NIH to do some specific work. I think in some respects we may be in somewhat of a protracted situation. We'll fill the pinch, but the protection we derive is the niche, the uniqueness

of our work. I think when times get tough if you have a special expertise that's hard to get outside, we may have some degree of protection from that, but we're going to feel the pinch.

I know the Office of Blood, for example, is working on developing some links for some product development science with NHLBI, which did not exist. OCTGT is developing links with NCI, and the key message to NIH is, you know, where your translational medicine stops the critical path starts. So that their success in having their basic discoveries translate into the bedside is only going to be enhanced by our success in the product evaluation science, both internally and creating the message externally.

So we're working on it, but I think we're going to feel the pinch. The same thing with the appropriated budgets.

I agree with you. I agree with Kathy and Harry on your point. I think we do have a niche as I presented in my slides, and we have a uniqueness, but in some aspects it can cut you the other way because one thing that we have felt is even the outside money has been in certain areas. So we have funding in the

bio-T area. We have funding in the pandemic area, but those are only two of the many areas that we deal with, and those areas we are filling a pinch.

CHAIRPERSON ROYAL: We have a question from Dr. Boslego.

DR. BOSLEGO: Is it correct that there's a Figure 2 here in that briefing material that appears to give a figure of about $5 million, say, in 2006. Is that the money that we're talking about in terms of research?

DR. BAYLOR: How much did you say?

DR. BOSLEGO: Five million.

DR. BAYLOR: Yes. I mean that's about where we are. We ill probably top that this year, by the end of the fiscal year. So you can see from the chart that that's the majority of our --

PARTICIPANT: This is non-salary, right?

DR. BAYLOR: Right. This is all -- as it says in the document, that does not include salary, but, again, salary goes for predominantly full-time equivalence. I mean, that extramural money does support some post-docs.

DR. BOSLEGO: And could you also say the first three or four external funders? What would they

be?

DR. BAYLOR: NIH, DoD, and I would say -- is DARPA part?

DR. BOSLEGO: NDPO.

DR. BAYLOR: NDPO, of course, of course. So as you can see, the top sources of the funding is actually coming from the department, from our same department.

CHAIRPERSON ROYAL: Dr. Shaw.

DR. SHAW: Knowing how long it takes to get any kind of a grant reviewed and the process and energy that goes into it, plus having to have it squeezed through the screen of conflict of interest, which is sort of an overarching concern throughout the government these days, has anybody ever taken a look at the yield of the process in terms of dollars invested in grant writing and nitpicking and so on and so forth and the money you actually get back? Especially if your total external funding is $5 million, Harry and I were here looking at each other, and we decided you can't blow your nose for $5 million these days.

(Laughter.)

DR. BAYLOR: But we do.

DR. SHAW: Well, yeah, but it seems like there ought to be a better way to do this obviously.

DR. CARBONE: Well, let me explain the process a little better. The good news is it's a 30-day process from start to finish for a grant review, and what we do is, well, I must say I modeled it after Hopkins, the research administrative process, and the investigators have done a great job in gauging.

We have a two-week turnaround commitment from the Office of the Commissioner. They have guaranteed us two weeks for the complete conflict of interest review and the appropriateness of the grant and the appropriateness of the budget.

What we focus on is an abstract, and it doesn't have to be the final abstract. So we always get that a month before the grants do, and the abstract is reviewed for exactly what Norman was saying, which is that we may have biases in our research program because of where the funding is, but we never want to extend outside the mission. So the abstract is used to identify that the project is within the mission in a high priority area.

We include in that just a budget for the FDA portion so that they know that, for example, we

aren't allowed to accept money for FTEs. So that's reviewed. So really the whole process is guaranteed, and as I said to Dano when we initiated it, we will never be the reason -- "we" being the grant review process -- will never be the reason a grant doesn't make it to acceptance.

Now, the good news is having come from a place where 35 page grants were the norm with RO-1s, and I'm happy to see my RO-1, and I transferred to my protegee and its' still going after 18 years. So I'm familiar with that process.

The majority of our grants are two or three page efforts. The NVPO is a couple of pages. Even the grants that NIH has, some of the targeted funds that we get from NIH are shorter proposals.

Now, that said, some of our targeted funds have been larger proposals, but they fortunately have come with larger amounts of money, and the fact is that we like extramural NIH just managed to get an amazing amount done with small amount of baseline resources, and these things are absolutely critical.

Investigators live in fear every day that if their research funds were to dry up, they couldn't do their jobs, not that they wouldn't be able to get

themselves promoted, but they couldn't do their regulatory job, but it's what we have to work with unfortunately.

CHAIRPERSON ROYAL: Dr. McInnes.

DR. McINNES: Norman and Kathy, I'm really struck. I mean I've lived and worked with my colleagues in the agency for many years, but I'm sitting here listening to this just thinking about the expectations that are placed on people and you're expected to be a credible scientist. You're also expected to be a generalist. You're expected to go and compete for dollars. You're expected to do regulatory review work.

And so what strikes me is, you know, if I could understand a little bit more around your tenure and promotion process, how all of that gets figured into knowing where some of those pressures are coming from, and I think down the line I know one of the questions you had was, you know, about equipment and retention of necessary staff.

In a way, you want turnover because if your science areas are changing, you want to actually have freeing up FTE dollars in order to be able to acquire the new skills that you need or you have to be

looking at alternative mechanisms and, you know, looking at visiting researchers, IPAs, all those sorts of things.

I'd during the day like to explore further how much effort has been made to establish a gift fund. I mean, the government can only take money through two ways. One is gift. The other is CRADA. And is there an opportunity to explore gift funds or a foundation way of doing business?

And I see the shaking of the heads, and I know the easy answer is no, and the easy answer from above is no, but that can maybe be made to change.

DR. CARBONE: Well, that document I said we sent to OC with four options, gift fund, foundation, using another agency's foundation, and in fact, we have another foundation from another agency that's willing to work with us.

The reason I shook my head with gift fund is that has been explored for decades, and for FDA, a regulatory agency, there is very much doubt that will ever be a mechanism. You know, a foundation, they are currently evaluating through our document, but keep in mind this is an officer of the Commission effort. It requires an active legislation.

And my understanding was the original NIH Foundation actually started as the FDA Foundation.

DR. McINNES: Ah, you see, you've got a leg in the door.

DR. CARBONE: Right. It estimates seven years for an FDA Foundation, and the Commissioner is looking at it. We initiated that process,b ut we do have a visiting scientist program. In fat, we're just rolling out a collaborative scientist training program at CBER with a full international regulatory body of scientists is likely to be our premier member, and the plan there is this is a dual part.

Actually these people probably don't know about it. It's still pretty drafty, but the document is done for circulation, but it's going to be a way of streamlining collaborations where if a collaboration is initiated, and we have over 100 now with different organizations, that an MOU will be created with an institution to sort of create the institutional bond, CBER to the institution. Within that program there will be individual projects, identifying individual collaborative scientists who will come here, and what this will allow is our investigators, rather than having to reinvent that contact will every time go to

these documents and say, "Here's our MOU. Let's get this signed. Here's our collaborative project. Let's get this initiated."

We have several visiting scientists, and in fact, we have just rolled out the formal SOP for that, which hadn't been in existence before I came.

DR. McINNES: So tenure and promotion?

DR. CARBONE: Tenure and promotion. We do clearly adjust the productivity for the fact that their time is taken up by other activity. So we do not have the expectation of productivity if someone's full-time job is science.

The second thing we do is I don't let them use impact factor because I don't care about something that makes of no value for the FDA, that gets into Science, but if something that gets into the Journal of Virological Methods that lets a product get through, that is a publication that we care about.

So we have discouraged, in fact, it's in the SOP they're not supposed to use at all impact factor. Now, that said, obviously they must be peer reviewed. It must be a high impact article that must be in a good journal, you know, not an online journal with no peer review, et cetera.

We do have standards, but we don't take the traditional scientific approach merely saying it's a great journal, it's a great article of impact for us. So we take all of that into account.

We have a seven year process for a junior investigator who's not a full-time FTE to become either tenured or out. They are mid-cycle reviewed by site visit so that they have time to be reviewed, given a message and fix their program if they need to.

The SOP is out for these scientists. It's called Service Fellow Pathway. So on day one, they can walk in and see what they need to have created as a portfolio in order to get converted at the end.

Our model, and then I'll turn it over to Norm, but our model for scientific expertise needs is actually somewhat extramural. Measles funding, measles expert. No measles funding, I'm an expert in another virus, another RNA paramyxovirus.

So what we have is people similar to -- the pertussis anthrax was an excellent example -- we have people who take the time and effort to, as the needs change, to mold what they do. I came in as a border disease virus expert. We are now the international experts on mumps mostly because nobody

else in the world or country I should say works on mumps, and that became our mission to do.

So we don't want to throw out a good scientist because they're in another area. We'd like to retrain them. The good news this year because of some external funding, we were able to give 108 training grants out to staff who were able to attend scientific meeting. They applied for it, and we essentially were able to fund everybody who applied and was approved by their office director, which has been very tough because training and education funds are some of the first to go, as you know, travel, et cetera.

But these were specifically for meetings for professional and technical expertise, and this was open to regulatory scientists, clinical reviewers, as well as the research regulator. So our goal is to make our staff as valuable and give them as much information as they can to be successful, but we definitely adjust expectations because of their jobs.

DR. BAYLOR: And it's the total package, Pam. So we look at all of the responsibilities of the individuals. So it's a total package.

I want to also say that because resources

are dwindling, we do have to sort of squeeze more out of individuals. So if you are a virologist, if you might happen to be a Herpes virologist, well, somewhere in your training you've studied viruses, and as budgets decline, we've had to pull people into other areas, and I think before the flu funding we were doing that, pulling people wherever we could and really broadening their responsibilities.

CHAIRPERSON ROYAL: Dr. Karron.

DR. KARRON: Yes. Just a point of clarification for that figure, too, that we were all looking at. I know Norman in the text it says that this excludes funding for pandemic influenza and bioterrorism, and obviously those are funds that are very targeted and restricted and may not serve the whole mission of the center, but can you tell me what then the total budget would be if you included those funds beyond the five million that you list?

CHAIRPERSON ROYAL: Yes. I really didn't want to get into that discussion at this time.

DR. CARBONE: He's looking at me because the tendency in all of these site visits, frankly, has been to drift into money, and the fact of the matter is unless we have a decent, sound, scientific

portfolio, we have a good method for identifying what we do and why we should be doing it. It doesn't matter how much money we have.

And the fact of the matter is we know and we appreciate the help and the interest and the comments, but the fact of the matter is we're working on it. We're delighted to see the comments, but we really would like people to focus a little more on the science. end of things.

We'll have time, too, in the closed session to go into a little more detail, budgets and whatnot if you want to.

DR. KARRON: No, it's just that if we're looking at a graph that actually shows funding, then I guess my question is really, I mean, we could just not ever consider funding, but if we're going to consider it or see figures that describe it, we should probably know what the total funding is.

DR. CARBONE: I think that the best thing, you know, we have appropriated budgets. It's very complex how it's budgeted because of our research regulators and how their salaries are funded. So we could go on in great detail and take a long time to explain that. Can I suggest that if we could pick up

a little more detail later in the afternoon, if that's okay.

I apologize for being pushy about this, but what we really would like to focus on is in an ideal world with all of the money possible are we managing our science well? Are we targeting the right areas?

Once we decide we obviously can't target all of the areas, then what are the priority areas to target? That would, I think be of great help for us.

DR. BAYLOR: I think, Ruth, your question is very important. You do need that context. I think we can discuss it later on today, but I think it is important for you to have that context in order to really understand where we are.

CHAIRPERSON ROYAL: I'll make my question the last question. We're running a little behind.

You mentioned earlier, Kathy, the fact that a few innovations and technologies developed here at the FDA have become industry standards. How does that happen? What's the process that's used to facilitate that and can it be improved upon? Are there some developments that should be out there that aren't?

DR. CARBONE: I would say the two major mechanisms are that we have a philosophy here that when we produce something that's good quality science that's valuable for product development, it must be put in the public domain. So there must be a publication.

The fact of the matter is people watch things that come out of the FDA and look at them whether -- we are often not the sort of main innovators of that particular technology, but we are the appliers of the technology, and that is viewed in the public setting and picked up by others if it's deemed valuable.

For example, neurovirulence testing, potency assays have been picked up, and the characterization of these HBOCs was not required. It just was a good method for characterizing them.

The second way is through the standard patent process which we participate under the HHS type rules. It's handled by NIH for us, and the advantage of having something patented is that it then becomes available for use in the outside world as well. Those are, I'd say, the two main areas.

CHAIRPERSON ROYAL: Okay. Well, at that

point we'll take a ten minute break.

(Whereupon, the foregoing matter went off the record at 9:58 a.m. and 10:13 a.m.)

CHAIRPERSON ROYAL: I'd like to invite everyone to return to their seats.

Okay. We are ready to continue on with our open Committee discussion, and at this time I'd like to invite Dr. Michael Brennan, who is the Associate Director for Research of OVRR.

DR. BRENNAN: Thank you, Dr. Royal.

I'd also like to give my thanks to the Committee members. I know this is a lot of hard work.

We're a fairly large office, I think the largest in CBER. So we have a lot of laboratories, and if you went through those annual reports in the back of the book, you know there's a lot of information there on some of the great work that our investigators are doing.

I think I'd also like to take this time at the beginning to also acknowledge that what we're talking about up here is based on the successes and hard work of the investigators, some of whom are in the back of the room here. Some of the lab chiefs will join us later during the closed discussion and

could give you more particulars on certain programs if you're interested in that information.

So if you can see this here, I just wanted to take this slide just to point out the position of the Associate Director of Research, and this position has actually been redefined. I started last June in this position in the Office of Vaccines and as you heard Dr. Baylor say, he's really only been in the position about a year. So the whole office actually is evolving and a lot of the strategies and management programs that we're putting in place for the research programs are new, and I think this is an important time for us to get your input on these management strategies for the research.

My primary responsibility then is to Dr. Baylor in the Office of Vaccines and to convey the research ideas and strategies and processes and priorities from the investigators through the division directors up to Norman.

But then also as Dr. Carbone mentioned, we have a new leadership council that has been mentioned by both her and Dr. Goodman which lies up here with Dr. Carbone as the Associate Director at the center level.

I also work then with her on trying to develop more crosscutting strategies for all of the offices across CBER, and then I have a lot of specific small duties within the office and the laboratory facilities, BL-3 help manage those things that are related to the research program. So you can see I had a lot of bosses and no power.

This was a little joke to tell you that we were going to be very open with all of our information. Maybe in response to the last question it's a little inappropriate.

So anyway, our mission basically can be broken down into two elements here. I look at it sort of as a gatekeeper element here to insure the safety. This is consumer protection, and in our office we have four basic products that we need to regulate: bacterial products, bacterial vaccines, viral vaccines, parasitic vaccines like malaria, and allergenic products as well, which lies within the Division of Bacterial Parasitic and Allergenic Products.

So we have this gatekeeper function, but we also have this function to be a facilitator, and I think here a lot of our research programs that are

helping to move along the development and accelerate the development of new vaccines through processes like the critical path that is now evolving in CBER through Dr. Carbone's leadership.

So research though can add to both of these major missions, and we've been using these, and I'll talk a little bit about these and give some examples of how our research program meets these principles. So we've been using these principles in the office as a starting point for how to prioritize our research efforts.

So our research programs should, one, address regulatory issues for our approved products, so the approved vaccines and other products that lie within the Office of Vaccines.

Two, the research programs should anticipate regulatory issues for new products. So we need to anticipate what's coming down the road here, and what should we be doing to get ready for this and what kind of science would help facilitate these new products.

And, third, the research program should respond to public health emergencies.

For these three in the next three slides,

I'll give examples from a research program of how the Office of Vaccine has addressed these three principles.

Also the research program maintains necessary scientific expertise within the office to meet all of the different responsibilities, both regulatory and scientific, development of guidance document, et cetera.

And lastly, OER wants to implement recommendations from external reviews, and this is a good example today of where we will get your ideas and then as we're evolving these new strategies for prioritizing a research program, for making two-year plans and five-years plans, and also how we're going to develop strategies for evaluating the research programs, which ones should be strengthened, which ones should change.

So this is an important element of our prioritization as well, and that's why we're here today.

So, first, the research programs to address these approved products. I've put down here two examples from bacterial products and two examples from viral products of vaccines that are approved. I

think historically one of our great stories of successes is in the acellular pertussis field which began more than a decade ago and led to the licensure in 1996 of the first diphtheria-tetanus-acellular pertussis vaccine, and our laboratories and our scientists within bacterial products, which was in the Laboratory of Pertussis, which includes Drusilla Burns and Bruce Meade and myself, had expertise in Bordetella pertussis, the organism that causes whooping cough, Drusilla's expertise in pertussis toxin and all of the methods, the pathways that lead to the secretion of pertussis toxin, et cetera, and Bruce's expertise in developing serological assays to the antigens that make up the pertussis.

And here the whole laboratory with the Laboratory of Pertussis moved parts of their research program into helping develop assays and methods for purification of the antigens that ended up being in the acellular pertussis development of monoclonal antibodies that were used as tools to characterize these assays, and these were all turned over to the manufacturers at that time, which actually there was 13 new products that came in in the beginning.

And there was also a strong partnership

with NIAID and with CDC to do this. And I think it stands still as a major PHS effort in approving a new vaccine.

And actually it continues today, particularly in Bruce Meade's lab with the development of human diagnostic assays that can diagnose pertussis in adolescents and adults, and last year we had two new acellular pertussis combination vaccines licensed for adolescents.

The second great example are the polysaccharide vaccines which also has a strong history in the Office of Vaccines, and it's based on the unique conjugation of polysaccharides to proteins and this method that was originally brought in by John Roberts, and then under the leadership of Carl Frosch at CBER up through last year until he retired.

And this led to the development of pneumococcal and we have four hemophilus, I believe, two pneumococcal, two meningococcal vaccines that are licensed. And so the laboratory there has contributed greatly not only to this polysaccharide conjugation method, but also to the human immune assays and the serotyping assays and now more recently, research on the outer membrane proteins of meningococcal.

Last year Menactra was licensed as the most recent meningococcal vaccine. So I think this is another really good example of how the research is closely linked to the development of products that are already approved or about to be approved.

And then viral products. We have the annual flu program. The research staff and the research program there led by Zhiping Ye is involved every year starting around November in the selection of new strains and development of seed stocks, as well as the development of the anti-sera which is going to be used to measure the potency of the new flu vaccine. So, again, every year this research program which also has its more basic research elements contributes to the development of the flu vaccine that will be used by the manufacturers and works closely then at the end stage of that process in testing the new vaccine that will be used along with the manufacturers in comparing notes on this for its safe and effective use each year.

And you have heard a couple of times now the other example which is the cell substrate initiative, which was begun with the safety questions around the cell lines that were used to produce the

original polio vaccines and also extends now to flu and looking to identify -- there's a number of investigators here, Phil Krause and Andy Lewis and Keith Peden and Arifa Khan who are bound to trying to develop well characterized cell lines or trying to identify ambitious agents that may be present in the cell lines that are used to make the polio and flu vaccines or the oncogenic potential of those cell lines.

So I think those are four good examples, and there are other that we could discuss later.

So in the second principle that our research is based on, this is using our research program to accelerate and facilitate the development of new products, which fits quite well into this critical path program, I've put down here the HIV from the Viral Products Division and the meningococcal and the tuberculosis vaccines from the bacterial products.

The HIV is work that has been led by Hana Golding and Surrender Khurana. This is based on a novel discovery of HIV peptides that are found in the HIV virus but not found in the vaccines that are being tested now in over 40 human clinical trials, and Hana has developed a diagnostic test based on a serological

ELISA type test that can then discriminate between individuals who have been vaccinated and infected, which is really important in these clinical trials for determining which people are really HIV positive and has a major impact.

Dr. Weir will talk about this a little more, but I think this is an excellent example. This test is at a stage where it is ready to be handed off to whoever needs it in these clinical trials, both manufacturers and NGOs and other groups.

Bacterial products. The polysaccharide conjugation technology led by Carl Frosch and Robert Lee and Cy and others in the polysaccharides group, a novel conjugation technology has been handed off through PATH, through the group that has developed this partnership for the development of a meningococcal vaccine that will work in the African meningitis belt, and this technology has been transferred to them to be made by a manufacturer in the developing country together then with clinical trials in various geographical regions.

So I think this is another outstanding example of how the research here in the office of Vaccines has led to the developing process of a new

product.

And lastly here, tuberculosis. Another really good example here is that Sheldon Morris and his group has developed or has received actually a CRADA to develop a post infection assay that will evaluate the safety of new TB vaccines that would be used in infected individuals. This is an element that could be seen as a roadblock to the further development of TB vaccines. Can we give these new sub-unit and live attenuated tuberculosis vaccines to individuals who are PPD positive who may carry an infection?

So he's now developing an animal model that can be used in the lab to screen these new tuberculosis vaccines for this safety parameter.

And, third, the ability to respond to public health emergencies. The two that are obvious that stand out are over the last five or six years our response to the counterterrorism and the development of both assays in the animal models that can evaluate new vaccines for anthrax and for Tularemia for plague and for smallpox and also immunological assays that could measure the potency of the new counterterrorism vaccines.

Dr. Walker will discuss this at some length. There's many different laboratories. I think this is a good example of where laboratories like the scientists who are working on pertussis have moved into a new field. For instance, Dr. Burns and Dr. Meade have moved into anthrax, and Dr. Weir has moved from his Herpes program at least partially into working on smallpox, and there are other scientists within virology that have moved to smallpox and other diseases.

The second example here, the most recent one is the pandemic flu, and the research staff within virology is now making plans to shift some of these research and resources towards making avian flu libraries, towards trying to develop non-egg based technologies for cultivating the flu virus and for trying to develop new types of vaccines, like DNA vaccines that would have a more broad cover.

So I think this is a good example here of where labs are shifting in response to public health emergencies.

So in addition to the priorities, there is a number of other programs that are supported by the Office of Vaccines, both monetarily here seen in

workshops and through the participation and core organization of OVR scientists in a number of workshops. I have shown four here. Two, the one on an assay of the potency of novel vaccines, and the one here, the TB regulatory workshop or co-organized by OVR scientists with NIH scientists and others, and these were focused on looking at critical regulatory issues, and for instance in the TV regulatory workshop invited all of the researchers that are supported by RO-1 grants and other grants from NIH to this forum to learn more about the regulatory process right from the start, from the IND process up through the BLA process.

And then the potency workshop that focused on this critical assay of trying to develop a meaningful assay that will be linked to the serological correlates of many of the vaccines that we produced and hopefully also to the efficacy.

Two other workshops are shown here that OVR has supported related to Neisseria and tularemia.

Another area where the Office of Vaccines is actively involved is in the global activities of the Center for Biologics. CBER is a WHO collaborating center. Two of the activities under this umbrella of

being a collaborating center is the international selection of flu strains each year and also within the office we have developed standards for screening the new tuberculosis vaccines that we distribute for free to investigators who are developing the new TB vaccines.

Another activity is for investigators to serve as expert advisors on WHO and PAHO panels. There are many examples here. Probably there's at least one example from every laboratory where an investigator has gone to Geneva and served on these panels to advise on either diarrheal diseases, enterics, to the development of guidelines, for instance last year a non-clinical and preclinical testing of new vaccines. There's many examples here where the investigators serve as temporary advisors.

Some of the investigators are the U.S. collaborators on the biotechnology engagement program with the former Soviet Union, and lastly, CBER has initiated a new global vaccine initiative about two years ago. The major purpose of this is to try to find ways to assist regulatory authorities in other countries in the developing world through the WHO to try to strengthen the capacity of those regulatory

authorities to develop the new vaccines such as TB and HIV, malaria, now the diarrheal diseases.

This is a major initiative where we're trying to do this without resources so far, and a lot of the responsibilities also lie within the Office of Vaccines.

So a slide about funding. Basically the sources of funding for OVR research, these are the four major sources of funding. The National Vaccine Program Office, in '05 we had six proposals that were supported by NVPO. This year we are receiving four, although the funds haven't arrived yet.

In biodefense related awards, this year we will receive nine from the Office of Research and Development coordination, which is part of the bioshield.

And interagency agreements is another source of funding for OVRR. One of the major ones we've had that has been a multi-year sourcing is for the cell substrates to look at the safety issues involved with the cell lines for vaccines, and this is with NIAID.

And the final source here is through cooperative research agreements. These are with

universities or other foundations. An example of one we have ongoing right now is for the post infection vaccine I mentioned before. It is supported in part by the AERAS Foundation, which is funded by Gates.

So this slide, basically I've tried in this slide to encapsulate how we evaluate the research program, and there was a couple of questions on that this morning. It's not an easy process to explain, but I've tried the best I could here. Although it's an ongoing process, we do this at least once a year on a more formal basis within the Office of Vaccine. The process actually begins in the divisions with the investigators. There's lots of discussions among the principal investigators and their research programs with the laboratory chief about the progress. They look at things like the publications, how many presentations were made, what type of outreach activities were participated in, what the regulatory work load was of each of the staff members in these research programs. This is discussed with the Division Director and then brought to the office with discussions with Dr. Baylor.

And then each year also in a process that we, to be honest, still need to formalize better

within the Office of Vaccines is a program where we need to evaluate current and the future regulatory needs. We have to look at what are the emerging issues, what are our plans for the next two to five years, and what recommendations have been made by external advisory groups.

And I think this is a process where we could use your input at this point on what you think are the critical elements here, and then these elements will be used then as an upper management tool to inform investigators what upper management is thinking about for the next two to five years to allow for the development of more strategic plans.

And we mentioned this morning that each individual is evaluated for promotions through the Promotions Committee at CBER, and Dr. Carbone talked at some length about this.

So I see our major challenges in the fiscal environment that we have right now as being these, and I think these actually are some of the challenges that we're giving you, the charge that was given you to think about and to offer recommendations upon.

I think within the fiscal environment we

have, although we have a lot of ideas that crop up from a regulatory mission, such as, for instance, the new topic of adjuvants, delivery systems like the use of the patch to deliver vaccines or transgenic plants.

These are the types of ideas we've been thinking about where, you know, that are going to come in the future or are already here and how do we address these types of issues in a restrained physical environment, which also then affects both recruitment and actually the promotion then of outstanding junior scientists up through our tenured track.

So these are things or challenges that we need to address. There are, as we have discussed already limited opportunities for outside funding. So we have to come up with novel ways to try to find external funding without changing the priorities of our regulatory and research mission as directed by FDA, CBER, and the office.

Travel to scientific meetings has also been restrained, and as well as things like training and sabbaticals.

And, lastly, communication of our research successes. How do we become more visible? For some reason, and I'm not sure why, a lot of our programs

tend to remain sort of invisible in certain niches within the scientific community. I think we have some reasons why that's so. There are some restrictions because we work at FDA on communication, but besides publications and presentations at meetings, we need to come up with more novel ways to tell the world what we do, as well as within FDA. Within the agency itself we have to show them the strength of our research program and why it facilitates the regulatory mission.

And, you know, communication is a keystone to managing and also to personal relationships. So we need to work on communication.

And my last slide. I wanted to use this slide. It came actually from the 1998 Science Board review of all of CBER, and these are some of the major reasons I came up why a researcher reviewer model was needed.

Following myself will be Dr. Weir to talk about all of the research programs within virology, and then Dr. Walker to talk about the programs within bacteriology, parasitic and allergenic products, and I think if you keep these in mind, you'll see many examples of how our research program has given us first hand experience with the latest technologies

that we can apply to the vaccine products:

The ability to assess the risk of new vaccines and therapies that are coming along;

Our ability to provide a timely response to emerging issues to anticipate future needs, to suggest actually new approaches in manufacturing, et cetera;

To help develop assays like the potency assay and the animal models for evaluation of new vaccines;

An enhanced ability to interact with PhRMA and with NGOs, with the World Health Organization and other sister agencies;

And also our research program gives us an ability to retain staff within the Office of Vaccines.

So I thank you for your efforts, and I don't know if we want to have questions now or hold them to the end after the others. Dr. Royal?

CHAIRPERSON ROYAL: I think we'll hold questions until after the next two speakers finish.

Our next speaker is Dr. Jerry Weir, the Director of the Division of Viral Products.

DR. WEIR: Thank you.

On behalf of the Division of Viral

Products, I would also like to thank everyone for coming today. I am going to provide a brief overview of the research and other regulatory efforts in the Division of Viral Products today.

I am going to divide the talk into two parts. In the first few slides I am going to give a brief overview of the division's mission, responsibilities and public health impact. There will be some redundancy here with what you've already heard and so I'll try to be as brief as I can, and then I'll switch to the overview of the division's research programs, priorities, areas of focus and examples of some recent accomplishments in impact.

Several years ago, we had a mission statement in the division that was about a page long and had eight to ten different bullet items. We have since reduced this to two fundamental aspects, two bullets that sort of from everything that we do flows from these two parts of our mission statement.

Basically what we do is to regulate viral vaccines and their related biological products to insure their safety and efficacy for human use and equally important we are here to facilitate the development of valuation and licensure of new viral

vaccines that positively impact public health.

The responsibilities that we have in fulfilling this mission are listed in this slide. They include the investigational new drug and biologics license application review, as well as other pre-marketing activities, for example, pre-INDs, meetings and reviews.

One of our responsibilities is BLA supplement review, lot release review and testing,a nd other post marketing activities. These include things like biological product deviations. People in the Division of Viral Products participate in manufacturer's inspections. These are both pre and post licensure inspections. We have a very active role in consultation with other public health agencies, in particular the WHO, but also CDC and NIBSC.

And finally, last but not least, it is one of our responsibilities to conduct research related to the development, manufacturing, evaluation and testing of viral vaccines.

So what is the impact of what we do? Well, I hope it's obvious or will be shortly, and I know you think I'm exaggerating by this little cartoon

I put up there that suggests that the people in the Division of Viral Products are what stand between the public and some sort of bird flu Armageddon.

But this is one area that I think it is very obvious what our impact is. I mean, it's not an exaggeration to say that on a yearly basis the people in our division are responsible for making sure that there's an influenza vaccine available, and the folks in our division do work with other groups in the public health service worldwide to actually try to insure that there will be a vaccine available should a pandemic ever occur.

But this is only one thing, and I want to stress this. This is only one area in which we have an impact. The fact is we regulate all viral vaccines, and these cover a wide range of diseases, and these vaccines are given to most of the kids in this country.

I have grouped them here on this slide by category. Hepatitis viruses, we have Hepatitis A, Hepatitis B vaccines, combinations with these Hepatitis A and B. We have regulated vaccines for vector borne viral diseases, such as yellow fever, Japanese encephalitis virus. We have DNA virus

vaccines, such as varicella, chicken pox as well as smallpox vaccines, other childhood virus vaccines, such as inactivated polio virus, measles, mumps, rubella, rotavirus we have just licensed again recently this spring. We regulate respiratory viruses. Of course, as I just mentioned, influenza vaccine as well as live influenza, attenuated influenza vaccines, and other viral vaccines, such as rabies.

But as I said, we're also responsible for facilitating the development of vaccines for other diseases. I listed a lot of these on this slide. These are, again, grouped by categories. There are vaccines that are under development for Hepatitis C, Hepatitis E, other vector borne viral diseases, such as Dengue, West Nile. A lot of vaccines under development for DNA viruses such as human papillomavirus, which you heard about yesterday; herpes simplex, cytomegalovirus. New smallpox vaccines are under development. New childhood virus vaccines, such as rotavirus vaccines are still under development. Obviously a lot of work to develop vaccines against HIV, other respiratory viruses such as new influenza vaccines are constantly under

development, including pandemic influenza vaccines, but also respiratory syncytial virus and parainfluenza virus vaccines under development, and a lot of work is ongoing for vaccines for emerging diseases and agents of bioterrorism, ebola, hemorrhagic fevers, other Venezuelan equine encephalitis virus and other encephalitis causing viruses.

The point of this is that there is still a lot of potentially vaccine preventable diseases out there, and it's one of our responsibilities to try to get such vaccines developed or to facilitate their development.

So in the next few slides I'm going to switch to an overview of the division's research programs, try to give you a little bit of background about our priority areas of focus and some examples of recent accomplishments and the impact of those accomplishments.

First, a quick snapshot of the division. There are currently seven laboratories, 17 tenured principal investigators; 67 full-time equivalent staff as of mid-April when I put this together; approximately -- actually there's more than 50 contract staff, most of whom are post doctoral Fellows

in the laboratories.

And as two quick examples of the success of the laboratory programs, I counted up approximately 140 publications in the last couple of years, and as I put some more background in your briefing booklet, in FY '05, for example, we had over $3 million in grants and contracts in the division.

So by and large the division's research efforts have been fairly successful by most criteria that you would use to evaluate them.

As you have already heard this morning, we are both researchers and reviewers. We do have a review work load that includes the things that I just mentioned, INDs, BLAs, post marketing activities.

The researcher reviewers in the division conduct mission relevant research,a nd as I said, we have a very active outreach and collaborative roles. For example, our expert consultants to WHO.

So what is the role of research in the Division of Viral Products? The research and the laboratory activities in the division complement the regulatory mission. We have already heard about that, but that is what we do. The program is designed to address issues related to regulated viral vaccines, as

well as to anticipate and address issues related to the development and evaluation of new viral vaccine products.

Sometimes these issues are general issues, applicable to many products or product classes. Examples of these would be cell substrate issues, improved test methods that could be applicable to many types of products, but we also address specific product issues. Sometimes these are correlates of protection necessary for efficacy evaluation. Sometimes they are the development, the evaluation, the understanding of the animal models necessary for animal implementation.

but in all cases the goal is to maximize the impact of what we do. To do this, we take advantage of the availability of the expertise that we have. We always address the appropriateness of the effort, in other words, whether we should be doing it, somebody in industry should be doing it, someone in academia is already doing it.

And of course, as you already heard several times this morning, we have many competing demands and we have to juggle many things at the same time.

The types of research activities that are undertaken in the division can be very applied, but they can also be fairly basic. The key is that they address issues related, as I said, to the products we regulate or the products whose development we are trying to facilitate.

The types of activities can include studies on vaccine safety, such as the evaluation of cell substrates. They can include studies on vaccine efficacy, as I've already mentioned, the identification of correlates of protection and the development of animal models predictive of efficacy. Some of our efforts are devoted to reagent preparation, particularly in the influenza field.

We also address issues related to the development and evaluation of new methods and assays for product characterization and issues related to vaccine development for emerging diseases. These include pandemic influenza again, but HIV, West Nile, agents of potential bioterrorism.

And again and finally, we also address novel vaccination strategies and technologies, things that we need to understand and be able to evaluate as products come toward market.

The layout of the division, the laboratories are shown in this slide. We have a small administrative staff of myself, my Deputy Director Phil Krause, and a couple of administrative people in the office, including a regulatory coordinator.

We have seven laboratories. As I said, these are roughly divided along product lines. I'll list them here and then talk in a little more detail in the next few slides.

We have a laboratory of hepatitis virus, with Steve Feinstone as the Chief; a laboratory of DNA viruses, with Andrew Lewis as the Chief; a laboratory of respiratory viral diseases, with an Acting Chief at the present time, Zhiping Ye; laboratory of immunoregulation, Ira Berkower as chief; a laboratory of vector borne viral diseases, Lou Markoff as Chief; laboratory of retroviruses, Hana Golding as Chief; and finally, a laboratory of methods development with Konstantin Churnakov as Chief.

Now, in the next few slides what I'm going to do is present two slides for each of these laboratories. I'm not going into a lot of detail, experimental detail about everything that they try to do, but what I'm going to try to get across is the

general areas of focus. I hope it will be obvious how those general areas of focus relate back to the products that they regulate and the products that are under development, and then I'll give a few recent examples of accomplishments and successes, things that have come out of these labs.

Most of the folks in the labs or someone from each lab is represented in the audience. So if you guys have detail questions later, I'm sure they would be happy to answer them.

So we will just go through the one by one real fast. The laboratory of vector borne viral diseases, the research in this group focuses on characterization of candidate live attenuated Dengue and West Nile virus vaccines. Also the mechanism by which flavivirus is repaired, attenuating 3 prime terminal deletions of genome RNA, obviously a safety concern for any type of vaccine of this nature.

Studies address virion morphogenesis, the effect of quasi species character on phenotype, and the development of an ELISA based potency assay for rabies vaccines.

Some of the recent accomplishments of this group include the determination that processing the

Dengue structural proteins, envelope pre-M and capsid requires the cellular enzymes signal peptidase. The identification of structures in the 3 prime noncoating region of the Dengue genomic RNA or acquired for viral RNA replication. A demonstration that the virus encoded RDRP contains an activity to repair the 3 prime terminal deletions of virus RNA, and a demonstration that specific mutations in the capsid protein abrogate attachment entry and uncoating in monkey cells but not in mosquito cells.

The laboratory of hepatitis viruses. General areas of research in this laboratory focus on vaccine strategies to prevent Hepatitis C infection; the development of mouse models for Hepatitis C infection to replace the chimpanzee models; the development of in vitro culture systems to study antibody neutralization of Hepatitis C. All of these are obvious examples of hurdles and roadblocks towards vaccine development.

The laboratory also addresses biomarkers for Hepatitis C protection and Hepatitis B/Hepatitis C related hepatocellular carcinoma; studies on rotavirus cell interactions and rotavirus attenuation markers.

Some of the recent accomplishments in this

lab include defining the pathogenesis and immune responses to Hepatitis C in the chimp model; a demonstration that protective T cell mediated immunity occurs in chimpanzees that spontaneously clear Hepatitis C infection; establishment that a neutralizing antibody to Hepatitis C does not play a role in the clearance of virus but can control viral replication in vaccinated chimpanzees; the establishment of in vitro culture systems in transgenic mouse models for Hepatitis C study; a demonstration that T cell vaccines can modify Hepatitis C infection and that CD-4 T cell escape is a mechanism of T cell vaccine failure; and finally, a demonstration that the N and C terminal regions of rotavirus NSP-5 are determinates of viral plasma formation and that VP-4 translocates to cellular peroxisomes by PTS-1.

The laboratory of immunoregulation. The research in this lab focuses on structure and function analysis of HIV envelope glycoproteins; vaccination strategies to enhance vaccine immunogenicity; and dissecting the neutralizing antibody response to vaccinia virus.

Some of the recent accomplishments in this

laboratory included the development of a novel method for performing virus-like particles and expression showing that expressed HIV GP120 and GP41 can be obtained at a lipid water interface; the identification of forms of GP120 with increased antigenicity and immunogenicity; the identification of a novel mechanism of resistance to HIV fusion inhibitors and the evaluation of the role of antibodies to A27 in Dryvax induced protection.

The laboratory of respiratory viral diseases. The areas of research in this laboratory include the preparation and distribution of influenza virus reagents to determine purity and strength of influenza vaccines. This group performs serology studies in support of influenza strain selection. They develop new high growth influenza virus strains for vaccines and determine properties for optimal growth in eggs and tissue culture. They evaluate new vaccine strategies and identify cellular receptors for respiratory syncytial virus and determine the antigenic structure of RSV glycoproteins. And finally, they focus on the development of serological methods for vaccine trial evaluation.

Some of the recent accomplishments in this

group include the preparation of potency reagents, strain specific anti-serum for seasonal influenza vaccine and possible pandemic strains. They have developed attenuated donor influenza virus that can be used for the preparation of pandemic vaccines, and they have demonstrated the improved efficacy of influenza DNA vaccines by co-expression of multiple genes.

They have identified amino acid motifs that contribute to high growth of Influenza B in eggs and demonstrated that heparin surface proteoglycans bind RSV glycoproteins, and they have identified binding domains that block that attachment.

The laboratory of methods development focuses its work on microarrays and other molecular methods for analysis of pathogens. This includes the genotyping of viruses and bacteria, identification of microplasmas and genetic stability of live virus vaccines.

They also focus on the development of immunological test methods, new animal models, and neurotoxicity assay development.

Some of their recent accomplishments include the identification of mutational hot spots in

vaccine derived polio virus; assessment of the mucosal immune response to IPV by direct PCR analysis and stool samples and vaccines; the use of block ELISA profiling of IPV to monitor consistency of IPV production and to study antigenic properties; evaluation of immunogenicity in new Sabin IPV and transgenic mouse potency tests; the development of rapid microarray based genotyping of influenza virus strains; the development of new neurotoxicity tests for mumps virus and the development of mumps virus neutralization assays for assessing protective immune responses.

This last accomplishment I'd like to digress for a second to show our flexibility. Most of you, all of you, I'm sure, are aware of the recent mumps outbreak in the Midwest. This is an example of something that in our own laboratories the development of this type of test.

Our response to this outbreak was to obtain sera samples from people that had been vaccinated with the aim of determining whether there was waning vaccine immunity versus poor neutralization of a different serotype.

So this is an example of how our expertise

and our flexibility have an impact on public health problems.

The laboratory of retrovirus research. Research in this laboratory focuses on the development of assays for HIV and smallpox clinical trial evaluation; the identification and characterization of adjuvants; the activity and safety of DNA vaccines and CPG oligodeoxynucleotides; the safety and evaluation of cell substrates used for vaccine production and retrovirus transmission.

Some of the accomplishments in this group include the development of a method to distinguish HIV infection from vaccine responses in clinical trials. Dr. Brennan mentioned this accomplishment already.

But also the development of a method for rapid measurement of neutralizing antibody following smallpox vaccination. In both cases these assays are very far along in actually being implemented and utilized in clinical trial evaluation.

This laboratory has also demonstrated that administration of CPG oligodexynucleotides preferentially activates interferon gamma-secreting cells, increases the antigen specific antibody responses and improves the protective efficacy of

pathogen specific vaccines.

They have developed assays to assess DNA oncogenicity and established induction conditions for detecting occult retroviruses in cell culture.

And finally the last laboratory, the laboratory of DNA viruses. Research in this laboratory focuses on the evaluation of cell substrates used for vaccine manufacture; developing methods to evaluate the risk posed by the use of neoplastic cells for production of viral vaccines; the detection of adventitious agents, mechanisms of latency; immunogenicity and preclinical efficacy of new generation smallpox vaccines and an evaluation of novel Herpes virus vaccination strategies.

Some of the recent accomplishments in this laboratory include the development of methods to evaluate neoplastic cells used in viral vaccine production, for example, tumorigenicity and oncogenicity assays. They have developed standardized quantitative PCR assays to detect specific polyomaviruses. They have developed novel methods for the detection of nonspecific adventitious agents and identified the major antigens of the humoral immune response to smallpox vaccination.

Other accomplishments include the demonstration that new generation smallpox vaccines elicit levels of protective immunity comparable to traditional smallpox vaccines in animal models of efficacy and demonstrate at the novel vaccination strategies result and can result in enhanced immune responses.

So in summary, I hope this overview has described how our research programs and laboratory activities support the regulatory mission in the Office of Vaccines in CBER with the goals of insuring the safety and efficacy of regulated viral vaccine products which literally go into almost every child in this country, but also are designed to facilitate the development evaluation of new virus vaccine products such that if a pandemic should ever occur, we might have more to protect ourselves in some flimsy gauze mask that was used in 1919.

CHAIRPERSON ROYAL: Thank you very much, Dr. Weir.

We'll go on to our next speaker who is Dr. Richard Walker the Director of the Division of Bacterial parasitic and allergenic products.

DR. WALKER: Thank you very much.

Good morning. In the next few minutes I'd like to tell you about the Division of Bacterial Parasitic and Allergenic Products. This is the other product division. It is very similar to what you have heard described with regards to the Viral Products Division.

I will follow a similar outline of the presentation and I will talk first about our mission and our structure to meet that mission and then go briefly through some of the science that we're doing.

Our division mission and functions is to assure safe and effective products for immunological control of bacterial, parasitic and allergenic agents affecting human health. Those three words, bacterial, parasitic and allergenic products, really mean a wide breadth of responsibility. For example, we have respiratory pathogens and sexually transmitted pathogens that are encountered by penetrating inoculation, like malaria, and then more recently, in the last six or so years we've been facing the challenge of being able to do regulatory review for special pathogens like anthrax and so forth.

And of course, we're not looking at products for every one of these possible things at any

one time. Things shift like there's really not a lot of activity in sexually transmitted pathogens right now, but, for example, we're seeing more submissions regarding malaria.

Further, things that we also have to deal with, diarrhea causing pathogens and other mucosally trafficking pathogens like the salmonella Type B, allergenic antigens, and then skin test antigens, and then more recently, something else we're seeing a lot more activity in is the live viral therapeutic products or probotics as they are known that may have various beneficial effects for people.

So we have to be very flexible to have a staff that can cover this breadth of products, and I'm very fortunate to have a very outstanding staff. In the immediate office, I have Milan Blake as my Deputy Director, and then we also have within the office a small regulatory staff, an administrative staff to benefit the whole division, and then the division is made up of six laboratories, the laboratory of respiratory and special pathogens under Drusilla Burns; the laboratory of microbacterial diseases and cellular immunology under the leadership of Sheldon Morris; the laboratory of methods development and

quality control, under Bruce Meade; the laboratory of amino biochemistry, that's allergenic products under Dr. Slater; and laboratory of enteric and sexually transmitted diseases that Kopecko leads; and the laboratory of bacterial polysaccharides under Willie Vaan.

Briefly, in these numbers in the case of Jerry's example, they change all the time, and so it's really about 80 people divided among the six laboratories. We have presently 13 tenured principal investigators and about seven people who are on tenure track, and the rest of the full-time equivalent staff in the division number 43.

Actually the contract staff is a rapidly changing thing. That's actually closer to 17 or 18 right now, but that was 13 when I made the slide.

The mission functions of this division is dependent on our researcher reviewers and the responsibilities that these people have is, of course, number one, to conduct regulatory review. They also conduct the critical research that you've heard discussed several times already.

Also as you've heard discussed previously, we serve outside organizations like WHO and other

organizations with subject matter experts, and then something that is becoming more and more necessary is we have to find outside sources to support the research.

The regulatory review and the laboratory work really is all one thing. In fact, perhaps instead of writing researcher/reviewers with a slash mark we ought to just make it one word, researcher-reviewer, because they're one thing, because the work doing the review and the work at the bench feed back and forth to each other.

And so we provide reagents and standards. We, of course, as you heard mentioned several times, we helped develop assays, and some of the assays we are using in industry now we're trying to improve technology. You've heard illusion to the conjugation technology. I think Mike mentioned that.

Troubleshooting, even licensed products, develop problems. It's not all over just when the thing is licensed, and so we have to have the expertise to work with the companies and troubleshooting the various things that happen.

And though all of this activity and research and also the review, we gain the expertise to

better anticipate the issues and try to fill those knowledge gaps that we see.

And then, of course, we provide expert advice to the industry and the vaccine community.

So the first of the laboratories that I want to describe is the laboratory of respiratory and special pathogens. Their areas of research as you might expect would include things like pertussis, anthrax, diphtheria, botulinum, and Yersinia.

And work falls into several areas: characterization of virulence factors, studies of mechanisms of action, gene expression, animal model development, more recently the plague animal model development, identification and characterization of iron regulated virulence factors, and mechanism of toxin entry into the interaction with various cells.

I'm not going to spend a lot of time with the history, but since one of the things we're looking at today I think is how things function and how the organization works, I think the laboratory of pertussis that began back when I was still in high school is a good example to look at. e had an expertise to work with the whole cell vaccine, and Mike has discussed this a little bit,b ut over time

unfortunately, there were adverse events associated with that vaccine.

And there was concern and consensus that it was time to develop an acellular pertussis vaccine, and then the existing people and other people were brought together as a team to address this problem, and they worked very closely together with industry almost as a team to address the issues such as antigen identification, model development, serological work and product quality assays.

One of the reasons I'm showing this slide though is to show how things keep evolving. Okay. So we had something to deal with a certain vaccine product. The vaccine product changed. We mobilized to help expedite that change.

But then after that was accomplished, we looked at things and made some changes within the organization. Based on the new product quality assays that were being developed we saw the value in having that kind of a resource applied to other vaccine products.

And so the laboratory of methods development and quality control lab was established to evaluate not only the product immunogenicity, but the

immune response to those products.

Also about that same time, the bioterrorism was starting to emerge as an issue, and so the pertussis lab became the laboratory of respiratory and special pathogens that I've just described that's dealing with the various issues, not only still with some work with pertussis, but also with these new agents that we have to deal with.

The laboratory and methods development and quality control, as I've already touched on, is established to develop quality control methods for bacterial vaccines, assayed methods for immune response measurement in animal and also to develop animal models for bioassays, for potency and toxicity.

Some of the recent accomplishments in this particular group are with the anthrax vaccine. I've been instrumental in an evaluation and optimization of the assays and to use in the clinical evaluation or in animal models to support the animal rule.

The anthrax vaccine posing new test development is involved in development of a mouse image density model and development of anthrax vaccine reference materials.

One of the things I want you to see from

this slide is that there's really no limit as far as the particular type of pathogen that this group might work with. Right now they are focusing on anthrax, pertussis, and diphtheria, but as you can see from the examples given here, we're looking at these products and how can we better evaluate them immunologically.

The laboratory of bacterial polysaccharides has people to do the characterization of polysaccharide conjugate vaccines, understand the confirmation of these antigens and how they are synthesized so that we can better evaluate the various vaccine products.

One issue that relates to safety is the role of Neisseria Island membrane proteins in disease, and so there's some work going with that, and interactions with polysaccharides with the immune system is also a key thing to optimize immune responses.

One of the highlights or some of the highlights is recently the people in this group have developed a DNA based method for serotyping pathogenic Neisseria; applied new NMR methods to the analysis of the carbohydrate confirmation of certain products; and something that Mike touched on just a minute ago was

the methodology for the meningococcal Group A vaccine. This is something that we have been working on this last few years. People in our division and in this particular laboratory have been studying the chemistry of the conjugation process and developed a way to greatly increase the efficiency of it, and this was just the piece that was needed by the meningitis vaccine project under the leadership of Marc LaForce to put together with the other components of his project to actually get a meningitis vaccine mobilized to Africa, and that is going into clinical trials I think as we speak.

The laboratory of microbacterial diseases and cellular immunology, they're evaluating the protective innate and adaptive immune responses to intracellular bacteria. Most of these diseases I've been talking about so far, of course, are not intracellular bacteria, and so antibodies are the key thing that we're considering there, but here we're looking at TB and tularensis so that we now have to consider aspects of how to deal with intracellular bacteria.

The work going on with the TB is looking at the technologies using live attenuated TB strains

and DNA vaccination in order to come up with better strategies against TB, and some work is also being done to look at antigens that might be important in protection against TB.

Mike has already mentioned the issue of working with the AERAS Global TB Foundation to find ways to evaluate whether the code response whereby somebody previously infected with TB upon vaccination might have a severe reaction can be determined. So this is a very important thing now and is actually a very exciting collaboration.

The laboratory of immunobiochemistry looks at allergin structure and function, also potency determinations. In fact, some work that was supported in one of our little in-group seminars this week was describing the new and exciting progress being made on microarray methodology for potency determinations. There has also been some work recently to evaluate the contamination or presence of endotoxins beta-glucans in allergenic extracts, which may have immunomodulating properties.

And also we're trying to understand how immunologic factors can help affect susceptibility to asthma.

Laboratory enteric and sexually transmitted diseases is looking at invasion mechanisms because some of these pathogens are invasive and also genetic regulation of bacterial virulence genes, mucosal immunology, dosing routes and everything because we need better strategies for mucosal immunization, and one of the very active areas in this group is developing platforms to deliver vaccines, and particularly some of this has been done with non-living cells, but a lot of the work has been done with using Ty21a, attenuated Salmonella, to deliver various antigens, and some of this work is used to deliver Shigella antigens, but some recent data shows that it also can be used to deliver the PA of anthrax, and as you can see in the chart, Ty21a by itself did not protect the animals against infection or spore challenge, whereas those that were treated with the Ty21a vaccine expressing PA were protected.

Also, this particular project is a good example of a collaboration between two laboratories because it was in the LASTC that they developed the product, but the Todd Merkel over in the laboratory of respiratory and special pathogens had developed the animal model for the spore challenge. So the two

groups worked together to do these studies.

The final thing that I want to touch on because I feel like by this time most of the other things have already been touched on is I think with all of this research going on it's very important to have adequate communication within the division, and I just want you to see how this process works.

Each of the six laboratories I talked to you about have laboratory meetings, you know, where they discuss what's going on, and they share information, and sometimes it's very productive as far as people finding out about things that are really helpful.

Like in one of the laboratory meetings, I think this was four or five years ago, it turned out that a lot of the work with anthrax was being stymied because the techniques to manipulate the genes and do gene replacement just really weren't developed and this was holding a lot of work back.

And so a new method of allowing exchange was developed as a result of this discussion, and the laboratory brought this to the attention of somebody who had the ability and some ideas about how to approach that.

So it's very important to keep talking about these problems at the laboratory level and then we also do it at the division. We have the work in progress which happened every week, and so people present the work there. The other people within the division and also from some of the other divisions come to these things and they can comment and make suggestions.

Publications, of course, are a big thing. We put out about 50 publications a year from this division. My review of the manuscripts, I get to see what's going on.

Actually reviewing the manuscripts, go into the work in progress that brought up a conversation among the lab chiefs several years ago about, gee, I mean, there's amazing things being accomplished by these people, and there ought to be a way to share this more effectively within the division and outside the division, and so we created something called the DBPAD update, which this next slide just shows pieces of the front page of that, and this is a quarterly publication we put out. It's not really just one page. You're seeing parts of the one page there, but this is the place where we get to share a

lot of exciting things that are going on.

And really, in fact, I'm not going to sell these to you, but you can see them for free. I put these back there in the back if you'd like to see them. They're about three pages of stories like you see highlighted on the front page on the slide, and then there's publications and other activities.

I think if you glance at these, you get a good breadth of the types of things and the scope of things that are going on within the division.

I personally am in awe of what these people accomplish with the resources that they have. So I think that gives you an overview without going too much into a lot of the stuff that has already been repeated.

However, I would like on behalf of the division and also on the office to thank you again for helping us do our jobs better.

Thank you.

CHAIRPERSON ROYAL: Thank you, Dr. Walker and Dr. Weir for those informative updates.

At this time are there any questions? Dr. Word.

DR. WORD: I'm going to address this to

Dr. Brennan primarily because it was on his slide, but it may go across all the divisions.

On one of your last slides you talked about some of the challenges. You listed five major challenges for management in your section, but I actually would just like to focus on the one. When you talked about one of the problems you had was promoting outstanding junior scientists, and the question I had was trying to get a sense of what percentage of people are affected by that and if you are having challenges promoting these individuals are you able to retain them, and if you're not able to retain them, then is there a challenge with trying to complete some of the other tasks that are part of the mission of the continued research and the review?

DR. BRENNAN: Yes, a very good question. Thanks.

I think this is something, you know, that has occurred over the, say, past six or seven years where in our tenure track in order to be promoted as a full-time senior investigator, the office in CBER has to provide this person with facilities and with assistance. Usually the critical mass is one research assistant, as well as a post doc, and what's happened,

because of our restricted fiscal environment I think over the last five or six years as it has been more difficult to do that. So it has been more difficult to expand into new programs, although there may be areas where this person has become independent and shown the expertise to grow in a new area that the office and CBER has decided is an area where we should grow.

I think we've been restricted in that ability to take the young people and move them into positions because of our restrictions on FTEs and those resources that must come along with the promotion of that person into a tenured position.

So there has been. Now, the numbers? I'm not sure. I don't know if we have good numbers on that. It may be that we have another program, a staff scientist program where a person can become a full-time staff person and still maintain some of the research within the group they were in and do at least a 50 percent regulatory work load, and some of those persons have moved into that type of a position.

Norm, did you want to say something?

DR. BAYLOR: I'll follow up on that. I mean, what Mike is trying to say is we're limited by

the resources of course, and so we may have -- so these individuals may not be able to become principal investigators. They may go and be hired as a staff scientist.

I mean, the limitations are because, as Mike said, we cannot provide those individuals, you know, staff, independent resources, but we don't necessarily just open the door and say, "See you later." We try to retain those people in other areas.

I mean, it's tough though because of the competition. I mean, some of these people will leave.

DR. WORD: I guess that's what I was getting to, was are we able to retain them more so than -- because I think you would probably find something if you could for them there, but how many of them would leave and then you're starting over again where you're having to train someone like in a particular research area or say how do you do a review, and you know, that starts over or it just gets shifted where somebody else may have to pick up the additional work. That's why I was just asking.

I thought you were going to say something.

DR. WEIR: I just wanted to add one thing. I listed how many principal investigators we had in

DVP, and I actually think that that's the same number we've had for every year that I've been the Division Director since 2001. I think we've lost one principal investigator and added one. So it just shows you things don't happen very fast in the sense of tenuring a lot of investigators.

DR. BRENNAN: I think another thing that happens that is maybe unique to a regulatory organization is that a number of the research staff also who come in as post-docs and do science also have the possibility of going to the regulatory division where they will have a full-time regulatory staff, and actually the research program sometimes serves as a bed of people that actually move into the regulatory divisions, which I think is a good thing because they have a good scientific background in a lot of areas.

CHAIRPERSON ROYAL: Dr. Greenberg.

DR. GREENBERG: Do you have data on how the average age of your scientists is changing or not changing? I know we try to keep track of that at Stanford.

Are your scientists moving up in age? Are you replenishing them with younger people? That's a critical question for your pipeline.

DR. WALKER: We're trying to on that one because in my division I can see that actually Carl Frosch retired just last January. We have another person who is going to retire at the end of this year. So we do have an actually aging generation of some of these researchers, and in the last few years particularly since I've been there, we've been trying to look for that middle management category of people and get them in there so that they can be the next generation.

But that is something that we have to be very aware of.

DR. BAYLOR: And let me just follow up. We don't keep -- we haven't kept hard data Harry, but we just look around at each other, but what we -- I mean, one of the top priorities in the office is to make sure when we fill a position, it's based on succession. So we want to make sure that the critical areas we've identified we have somebody in place to take over if that's a critical need. Then that's the top priority.

DR. CARBONE: I think an example of that was the flu program where we suddenly lost an investigator but had five years earlier hired a tenure

track principal investigator to work with the person with the knowledge that there was going to be some movement, and now there was an opening and another investigator, a junior investigator is going to be hired or another principal investigator.

So every attempt is made to do that, but it's a little restrained at the resource center.

CHAIRPERSON ROYAL: Dr. Hewlett.

DR. HEWLETT: On this same issue of recruiting, I was going to ask what it's like recruiting someone into these positions, and then I realized at least from the ones that I know about there's a lot of people that are there as Fellows that as you just described that move up in the system rather than being recruited into a tenured position from outside.

That's generally the case?

DR. CARBONE: We have both. I think that the advantage from the inside is the regulatory training. Virtually it's hard to know if somebody will be a good regulator since almost nobody on the outside regulates, but we have had several people; several lab chiefs were brought in from the outside. So it's really a mixture.

It's nice in a sense to have that cadre of trained investigators, but keep in mind they compete on an equal level with all outside candidates for positions. It's not an automatic situation, and the peer review is done on individuals both internally and who come in externally if they're going to those positions.

So we try to get the best person for the job.

DR. HEWLETT: And how do you feel about your ability to recruit, given the limitations that you've been describing to us?

DR. CARBONE: Well, I think we have a harder time. I'd like to see an easier time. I'd like to see a greater -- we try. We advertise, et cetera, but you can speak to that as well, Norm.

DR. BAYLOR: No, I was going to say it's tough, I mean, especially at a senior level, but at a more junior level, I mean, we do have an attraction, and that's being a regulatory agency, you can see, as I've commented earlier. You are exposed to the field and what's going on from everybody. So that's a huge advantage, but I think that individual coming in has to be somewhat flexible and not necessarily think that

they will have a permanent position at the FDA.

They may, but depending on resources, they will be, I think, highly trained to compete in other areas, especially having the exposure that they have received here.

DR. BRENNAN: I think another thing, Eric, is this question of visibility. You know, it seems to me a lot of times when people come in and see what we do and the extent and quality of our research, they say, "Wow, you do that?"

And so that's another issue I think we need to address. If we could address that outside external visibility a little better for our research programs, I think it would help our recruiting.

DR. HEWLETT: I agree with that. I must say one of the things I've been thinking through all the presentations is that the general press, you hear lots of critical things about how slow the process is and you all know this better than I do,b ut it made me think that maybe some sort of PR for your agency because you do -- I have the same feeling.

I visited Alan Shaw as part of our biodefense program. We went on a tour, spent some time at Merck a couple of years ago, and I felt the

same way when I left that experience, that there is incredible number of hard working, dedicated people, and that doesn't come across to the public.

I wonder if there's some way for that to be the case, both for the regulatory part and for the research.

DR. BAYLOR: Let me just add on a small scale we are trying to get out more. We've recently hired a communications special assistant to our office. We're working with the press office to try to get out good news stories. I mean, we should have done this 100 years ago, but we're trying.

DR. BRENNAN: We should have Dick stand out at the Metro stations with his DBPAP newsletter.

(Laughter.)

CHAIRPERSON ROYAL: Dr. McInnes.

DR. McINNES: Knowing how I think successful CBER and these groups have been at developing tools, methodologies with diagnostic potentials, et cetera, down the line, I'm trying to understand how aggressive the licensing piece of the house has been.

Is there an unexplored avenue for licensing technology out and thereby earning royalties

and thereby being able to fund your research programs?

DR. CARBONE: Actually Dano Murphy who is the lawyer who works with me, his plan this year is to put out SOPs for this center on MOUs, MTAs, IP approaches so that everybody will be clearly -- at least the first step is to educate everybody that these processes exist and then how to engage.

And the next step, once people have a clear idea of how to engage, then the next step, of course, can be to make sure people engage appropriately.

We have actually also to reconsider the criticism. Why is the FDA participating in patents? And there are other issues that we deal with. Now, our approach has been, and we have even heard from industry supports this as well, that once something is patented, it can be licensed, it can be accessible.

So that's a good thing, and so that is in our plan to make sure that's clear. We go through the NIH system, but I think our staff in terms of MTAs, materials transfer agreements, and IP is not as educated as they need to be. So that's going to be made clear.

DR. McINNES: It just strikes me as an

untapped possibility that you really could be growing some of that potential and, you know, if you even got one out of ten out there, you'd be so much better off just in terms of financially you would be better off in terms of funding your internal research program.

DR. WEIR: Just to make one quick point about that, you might want to remember that if royalty money does come in, it, of course, doesn't get spread evenly across either the division or the office. It goes to where it came.

DR. McINNES: Well, in the NIH model it's very clearly articulated. I mean, in terms of an individual can benefit from it, but then there is a pool of resources that can be used across, and it's at the director's discretion.

So I think there is some flexibility there for both personal reward for the inventor as well as for the whole organization.

DR. CARBONE: You're right. Actually as it's designed, the laboratory identified in the patent is CBER. Now, CBER has historically done what Jerry says, sent the patent royalties to the laboratory support of the individual, but officially we could go through another model because CBER is the identified

laboratory. So there's flexibility there.

CHAIRPERSON ROYAL: Dr. Shaw.

DR. SHAW: Yes, this discussion of patents and intellectual property reminds me of a larger issue within the vaccine industry and CBER, both, and that is that the biggest effort at least in my experience in developing a vaccine or any kind of a biological product is not making the product itself. It's testing it, and the testing load, the testing expense, the complications of testing, of biological entities in general are fraught with statistical difficulty and everything else.

So once an assay is developed by CBER, how is it put into play in a way that it's officially accepted and sanctified and homologated and all the other stuff that goes on? I mean, you can cite examples of things that were developed at least partly at CBER that took forever to get into practice if they ever did, like Konstantin's MAPREC assay, you know, and all the stuff for polio. That was developed back in what, the late 1980s? And it's just now being accepted at a point where a lot of people are no longer using polio vaccine or at least not the live one.

So you know, this takes a long time. Is there a way to make that more effective?

DR. CARBONE: You're absolutely right, and we have to walk this fine line because you don't want an acquired assay that isn't officially -- validated is fraught with all sorts of baggage. I use the word "qualified."

And so there are mechanisms that would engage into trying to get assays qualified, but sort of the international process, et cetera, can be quite lengthy.

The big picture is that we often will put out the information and say to a sponsor, "We need to know this with this much certainty," and then they will come to us and say, "We propose this," and we'll say, "That sounds like a good idea."

So to dictate you must use X, Y, or Z may not be always the best approach. Now, having something available for people to use that they can use with certainty is a good idea. So I'll pass on some examples.

DR. WEIR: Yes, if you don't mind, I would like to ask Dr. Golding to come up here. She has two recent examples of things that were developed in her

laboratory, and I think they made a fairly rapid transition to the clinic.

So she can tell you how the process worked.

DR. GOLDING: Actually, I think this is extremely a very excellent question, and it's something that is very dear to my heart because ultimately why do we make this effort to develop this assay?

We really want to see the benefit of the vaccine trial as rapidly as possible, and I would just like to mention two assays. The first was actually the high throughput report of base SA2 measure and neutralizing antibodies against vaccinia that can be used now in a semi-automated way for evaluation of new, safer smallpox vaccines.

So once this assay has been developed, what we did we actually transferred the under MTA to a central lab that was chosen by a working group of the Niaid, initially in New Jersey and more later actually in Texas, whereby we under MTA provided the assay. We gave the training for people who were sent to our lab for both of these, and then continued as consultants.

So this was done actually for no benefits to our lab directly, but it has already been implemented in those central labs that are evaluating new smallpox vaccines, including the MVAs that is now a very strong candidate.

In the meantime, industry that was interested in using this assay for evaluation in house of their vaccines, all vaccinia immunoglobulin, like Cangen and Vaxgene, they also through the IT office paid for a limited licensure and then sent people to our lab to learn the assay, and we provide them at the same time with stock virus, with positive control, with VAG standard reagent and helped them to basically set up the lab.

I would call it a relatively rapid transition from our lab to the regulated industry and to sponsors. What happened now is our new HIV selectors, we've just reached that stage, we've just reached the level of sensitivity and specificity that IAVI, the HVTN and other Office of AIDS Research are very much interested in starting implementing it in better sites in Africa and the United States.

So through probably the mission on heart and lung, there will be an RFP to identify a GLP

facility to which we will again transfer under MTA very clear SOP, how to make the plates, how to drive them, how to make them both for shipment and storage, and how to run the assays.

And there are at least one or two companies that are already sort of forward looking because the potential of implementing in blood banks and others, and they already inquired about acquiring either a limited or unlimited licensure. And I think this will move relatively quick.

DR. WEIR: And I think we've had other examples in the past. I mean Dr. Chumakov's lab developed transgenic models for polio virus, and I think WHO adapted those. So I don't know whether the time line was similar or not.

DR. WALKER: From our side, I know that there are some products or some tests that are being used by certain industries now, and I don't know the history of exactly how fast those things moved along, but they have -- the technology is getting transferred.

CHAIRPERSON ROYAL: I have a question. To some extent it seems as though some of the labs at the FDA provide sort of reference lab type functions. Is

there compensation for that? Are there fees levied that have to be paid?

DR. BAYLOR: Unfortunately not. I mean, I think of the activity and the resources that we spend in our influenza lab that we have spent over the years preparing reference reagents. We get nothing for that, but the satisfaction of, you know, protecting public health.

CHAIRPERSON ROYAL: Again, that seems to be a missed opportunity for at least that activity to be reflected in the budget to support that sort of thing.

Go ahead, Jerry.

DR. WEIR: Well, I was just going to mention along those same lines, whereas we make influenza reagents every year, antisera and distribute them, the rest of the world gets them from NIBSC, for example, does pay for them.

CHAIRPERSON ROYAL: Yes, Dr. Boslego.

DR. BOSLEGO: I have a question for Dr. Weir and for Dr. Walker.

In regards to the mumps outbreak, were you able to, you know, with the research you did regarding the evaluation of the strain, were you able to make a

conclusion?

DR. WEIR: I'm sorry. Were we able to?

DR. BOSLEGO: Make a conclusion regarding whether this was weighing immunity versus a new serotype.

DR. WEIR: Actually this is Dr. Carbone's lab. I think the studies are just starting. Maybe she could.

DR. CARBONE: And I promise you I had nothing to do with this outbreak. I did not manufacture this.

We actually were contacted by the CDC because we have some expertise in the serology end of things, as well as in viral investigations looking at the relative virulence of different wild strains of mumps and vaccines.

The bottom line is it's all in process. But we have plans to look at antibody avidity, for example, as evidence of primary or secondary response, and people we know have been exposed. We also have several hundred sera from individuals who have not been exposed. They were in a remote site, but we have good data on two vaccinations, and they received their vaccinations, and so the plan is to look at

early, "early" meaning literally weeks after vaccination.

We're working collaboratively with industry, as well, on this, early vaccination sort of several years out and then extensively out to look at those, and people we know were not exposed.

We're also planning on getting the -- we have now actually the serotype circulating, distinct from the vaccine serotype, which historically never was believed to make any difference, but we're going to be looking at in particular low levels of antibody. There may be some hint of serotype making a difference in immunity, but that's completely hypothesis, and so we're going to be looking at that as well.

So we're closely collaborating with Bill Belini at the CDC on that.

DR. BOSLEGO: You do have the strain that's circulating.

DR. CARBONE: Yes, yes.

DR. BOSLEGO: Okay, and Dr. Walker, it's really the same question related to pertussis. With the increasing incidence of pertussis, has your lab been involved at all in investigating that?

DR. WALKER: Do you want to comment on that because this is something that Bruce's lab would be directly involved in.

DR. MEADE: Well, we have been working --

MS. WALSH: Excuse me. Can you just identify yourself?

DR. MEADE: Sure. Bruce Meade.

MS. WALSH: Thank you.

DR. MEADE: Yes. We've been working with the colleagues with CDC for a long time, and actually they funded us to bring in a post-doc for a couple of years to work on -- we have known for a long time how to do diagnosed pertussis serologically. You know, we sort of know how to do it, and are translating that. So that has been a project we've been working on and made pretty good progress to know how to do that.

And the goal is to take the methods and actually transfer them back to CDC because we have to follow our research on the subject of rules. I mean, we can't until it's appropriately validated in terms of doing clinical diagnostics, but it's a transfer technology to the CDC lab. So we've been working with them.

Again, there are outbreaks as you know

going on routinely, and they're very anxious to get this implemented to help with the diagnostics.

CHAIRPERSON ROYAL: I may have missed this, but could you state your name again for the Board?

DR. MEADE: Bruce Meade, Laboratory Methods Development, Quality Control, Bacterial Products.

CHAIRPERSON ROYAL: Thank you.

Dr. Hewlett.

DR. HEWLETT: I'd like to come back to the resources issue, and I won't ask about money. You mentioned, Dr. Carbone about core facilities, and I know having extra mural funding is important. IT sounds to me like you are able to provide a big component that's important to laboratory research by virtue of having core facilities. I'm aware of some of them, the BL-3 space.

How extensive is that? Do you have a budget specifically for that that are shared facilities for a large group, and does that include paying, for example, for animals and other resources that are needed for the laboratory research?

DR. CARBONE: That's a great question.

I think in our -- what is that phrasing you used? That was very good. Was budgetarily restrictive or fiscally, fiscally, fiscally restricted. The economy of coordination and cooperative and avoiding duplication is critical. So what we can do as a center to save money, working as a center, we do it and I'll give you some examples.

Our investigators are required to purchase the animals for research, but the center covers the animal care thereafter, including primates. If someone has, for example, an outside grant and this involves an effort that is related to but distinct because of the grant, then we do ask for the care costs to be provided, but for work done centrally we provide that.

The core is provided solely as an FTE support. We provide a certain number of FTEs, and based on charging back to them and to the external world, several external sources use our core. They have access to that at very reduced cost, and I asked the corps director last year to do a budget analysis to make sure that what we were doing was economical, and it was fairly well proven to be a good bargain.

We also do the BSL-3s cooperatively, but

the offices are required to staff and provide equipment. Our flow facility, for example, is partially center supported and center coordinated. We have all of the offices combined put the large flow and sorters in one room.

Actually one of the offices donates an FTE, and we all get together to cover the service contract, including center support. Mass spectroscopy is the same thing. So we basically have a strategy where if a piece of equipment is over $100,000 and is documented to be utilized by several offices, at that point we coordinate and share in the cost and the center tosses it in.

So wherever we can get the economy of scale, we try and do that.

CHAIRPERSON ROYAL: I think that's an excellent way to accomplish what you're trying to. So basically you would consider this subsidized fee for service.

DR. CARBONE: Of the core? Yes.

CHAIRPERSON ROYAL: Okay. Dr. Greenberg had his hand up.

DR. GREENBERG: I think Dr. Goldman was up.

DR. DOLIN: Well, gaston. I wanted to ask you to help clarify for us how decisions with respect to priority are made, strategy. You have the Research Leadership Council in place. How are decisions made as to prioritization of resource and facing the contingencies of even more fiscal constraints?

It's not clear to me how that's done on a regular basis. Maybe you can help us understand.

DR. CARBONE: I think what I'll do is I'll start with letting the office directors because the product offices drive what their priorities are, and Dr. Goodman and I look at these and coordinate across the offices and then add in priorities based on Dr. Goodman's experience in the large world and other agencies.

But our real focus is product. So we start with product specifically. So I'll hand that over.

DR. BAYLOR: And as I said, the Office of Vaccines is the largest office in the center.

I didn't show it. I think you have it in your book. I didn't show the slide, but when we look at our regulatory work load in the Office of Vaccine, it's pretty intense.

We have approved probably more products; I know we've approved more new BLAs than any office in the center, and we have six BLAs pending. We have approve five or six. I can't remember the exact number, in the last year.

Decisions are made, and Kathy can get into this, how our appropriated funds are allocated to us from the Center Director, and so we have that pooled money coming into us from the center. I meet with the Division Directors, and they also discuss with their lab chiefs what really are the needs of the office, and we sit, and again, the needs are driven by the regulatory. What's in our pipeline? What's coming down the pipeline?

And we evaluate sort of our portfolio and decide where we're going to fund certain areas. And, again, we're talking about a very limited amount of money. So recommendations are coming from the division directors to the immediate Office of the Director. These are our needs.

I asked for budget from each Division Director. What are your needs for this period? Again, we're dealing with very limited money.

They also take into consideration -- and

they can comment on this -- they can take into consideration what kind of external funding is coming into their areas. I'll give you a great example in the office.

I feel that the work that's being done in the allergenic extract area is of a high priority. That area is not as well funded from the outside, but that's the critical area in the office. So we have to look at that as one example and say, well, this is an area that is high priority. We have to fund that one with appropriate money. We have to adequately supply or support that with appropriated money.

So we go through sort of discussions, internal discussions and decision trees to allocate the appropriated money. The Division Directors, the investigators who are bringing in the external money, they control those funds. What we control is what funds can they go after.

So we will not allow an investigator to apply for a research grant working on a snail dotter or something like that. So there is an evaluation process, but they generally control those funds.

Jerry or Dick, do you want to comment?

DR. WALKER: That allergenic example was a

good one because that's one of those areas that doesn't bring in a lot of external funding like something that's dealing with bioterrrorism, and so what I do is I meet Dr. Slater and some of the other people that are dealing with not only allergenics but some of the other areas that are not going to be well funded, but we have to have, and we figure out what we need there, and I put that into the budget plan that I go to Norman with, saying that we want to get these funded and then whatever else is available, then we'll deal with the laboratories that have more external funding.

And so we try to make sure that, you know, things like allergenics gets funded and they're talking care of just because I know they don't have extensive outside resources.

And so we work that out, and that's a block that I bring to Norman and say, "We've got to get this funded," and then the other groups that get a lot of outside funding, you know, that makes it a little bit easier for them, but we still need to help them with the internal funds, too.

DR. WEIR: I don't have a lot to add to that. I mean, we sort of view it as a two-way street

at every level. I mean, we take advantage of the individual investigator's expertise to know what's important in their area. They sit down and discuss it with their lab chief and prioritize at that level and interact, and then the lab chiefs do it with me, and then I do it with Norman and so that we're trying to cover all the bases so that we can take advantage of everyone's expertise and yet at the same time try to see the bit picture.

DR. CARBONE: So let me rephrase that in this center sort of SOP process. I'm a big person to bullets and outlines because they're simpler to comprehend.

So the first initial step with the Research Leadership Council is formalizing this process and making it very transparent, and the first essential step would be for the center director to identify the broad brush areas of importance, and I think you saw some of those, Jesse Goodman. They're not rocket science. They're what faces us in huge public priorities.

And then that will be communicated down to the offices. Then the offices would be expected to go through their process, and part of the formal bits of

the process we've identified is a formal connection and discussion with the regulatory scientists/leaders and staff to gather their input and their experience.

And we have a plan and some suggestions to, for example, capture what we do in IND review. For example, you would capture what are the critical path issues in research that are brought up by this IND. So we get details throughout the year and collate that information.

To look at the regulatory workload, as was said, we have to cover the vaccines that are out there, and our research should be well enough matched to our regulatory needs and the current needs, as well as anticipated needs, and then the staff and leadership from their expertise and experience would also identify critical areas, and this would be the knowledge, for example, that bacterial products need allergen support. So the data would essentially be captured.

Now, we have the data, what people are doing, since we have the research program reporting, and in that they proposed what they're planning to do, and they provide their outcome for the future.

So taking that information, then

individual programs would be identified as good output, on target, highly meeting with prior needs, or no output, off target, et cetera. And budgetary decisions would be made within the office.

The office would present those back to the center director for review. The offices would also discuss with each other since we don't want to see too much duplication, unnecessary duplication. Sometimes duplication is necessary.

And that, again, is the center function, is to help the offices get together and coordinate across the whole office the research program, and Jesse would review; Dr. Goodman would review the proposals and then we would go off, and then this would be envisioned as a -- I left this slide out of my presentation. We have a little circular diagram which sort of describes this process.

And we're codifying that with all of the offices, and the offices are part of that codification.

DR. BAYLOR: I think you really need to keep in mind that we're talking about a very small amount of resources, and also the operations, that takes a chunk of the resources as well. We are

responsible for -- and I don't want to get into this too far -- but we are responsible; our office is responsible for the testing laboratories also, and they are in our office. The majority of the testing is Vaccine's, but we do testing for the other offices as well. So that comes off the top. That has to be funded.

So our other things are eating upon those limited resources besides research.

CHAIRPERSON ROYAL: Dr. Greenberg.

DR. GREENBERG: Thanks.

I'm still not clear how you are actually planning to implement the cross-cutting or interdisciplinary approaches to the program. It strikes me that you're organized pretty much the way a classic academic institution is organized. You have what we might call either divisions or departments, and they have been there for a long time, and they are working reasonably well.

But I don't see a good mechanism. I'm still not sure what exactly the mechanism is that, for example, where you can use the expertise across all these divisions for, let's say, vaccine safety, immune response, a whole variety of things that actually have

to do, and this is not unique to you. I think almost every academic medical center is trying to figure out the exact same thing.

Most specifically, I don't have an idea of who you're going to do it without some amount of support for the cross-cutting activity. In other words, all of your funds flow seems to be directed in a divisional way. How do you move it when you want to direct funds that are actually moving across those?

DR. CARBONE: I think you're absolutely right, and that's something that every organization struggles with. In fact, I heard yesterday there's an organization that is working to break that down and apparently has done so successfully. So I have a phone call note to myself, "Call so-and-so."

But the center director is taking a role in trying to coordinate amongst the offices, and what we've actually developed in some cases are teams essentially that meet and discuss.

And one example was SARS. When SARS hit, you know, sometimes we get lucky, and we had somebody who had actually done a post-doc in corona viruses in a very good lab and had a very good track record in corona virus, and so suddenly she became our SARS

expert.

And we got together all of the offices that might be effective, and we sat down and met several times over a series of about a month, and we determined that in blood there was going to be a concern with SARS in the blood, and what's going to happen to the blood supply. In other words, what are the problems that are going to occur with the SARS vaccine?

In fact, if you look in the literature, somebody in Blood had now written a little editorial on what are the critical issues in SARS vaccine development, and so we identified some of those.

Difficult to inactivate the virus. It's a very environmentally stable virus, and this inactivated vaccine is going to become an issue, et cetera, et cetera. So we had a list of about ten issues we identified there.

And then with OCTGT, not so much with SARS, but they participated. So in the end, we sort of asked everybody, okay, what is each office. How are they going to attack this problem from a research point of view?

And everybody put together a little

proposal that said, "This is what I think we should do," and it turned out there was overlap, and what happened is we decided that the vaccines person who had experience with the live virus would now serve as the person who would do all of the neutralization assays for the entire group because she had a coordination with NIH. She lost that, and then it ended up we could contract out.

So the centers provided the money for her to contract out these neutralization assays to answer questions across the center. The people from Blood determined they were going to look at some immunogenicity and epitope, which of course would help vaccines, but they're the antibody expert. So they were going to look at IVIG and what antibodies might be available for therapy, et cetera.

So this is an example where we got them together and they coordinated, and in terms of the Research Leadership Council when we formed that, that's exactly what I said, Harry, was how are we going to put our money where our mouth is?

So we actually have through some begging, borrowing, and stealing internally pulled together funding to support cross-center, high priority efforts

that involve strengthening essentially technological areas where we are weak across the center, boosting programs that would benefit all three offices.

So the proposals will require clear cross-center benefit and participation by several of the offices, and we can back that up with a little money at least for the next couple of years.

So we are really at the nascent stage of formalizing the cross-office network in terms of developing these teams. So the plan, we develop the teams, get the teams together in regular meetings, get them to engage in prioritization, reducing duplication. That's all to come, but those are the plans.

But we o this informally. I've already begun the process.

DR. GREENBERG: I would just say that from working in groups, if you need the buy-in of each one of your current existing organizations to understand how they are benefitted in a constrained environment, the key is to show how what you're doing helps then.

DR. CARBONE: One good thing is actually Vaccines was one of the leaders in this idea. It was Mike Brennan who first brought this concept to the

table. So I think, I'm hoping that we'll have an easier time getting some good office buy-in.

DR. WEIR: I wanted to speak to this at the division level at least, about the cross-cutting issues. Again, it is always issue driving, but within the Division of Viral Products, of course, we have examples of this. The one that's the most notable over the last few years is the general issue of cell substrates, and here we have a number of researchers with various types of expertise who have come together and worked with NIH actually to address a host of just broad issues related to the use of cell substrates.

So that's one mechanism that doesn't depend on the internal, traditional funding thing, and as Kathy alluded to, we're doing something inner office related. Actually this inner office related that addresses more general issues related to all development of all biodefense type vaccines. So it does happen.

CHAIRPERSON ROYAL: Dr. Hewlett, I believe. Oh, Dr. Tacket.

DR. TACKET: You almost answered my question. I'm also interested in not only cross-cutting teams within FDA, but what are the mechanisms

for you all to work with the other federal agencies, in particular CDC and NIH on the bioterrorism issues and the pandemic risk issues. How do those communications go on and how are you sure that you're not duplicating and that you're synergizing, et cetera?

DR. BAYLOR: I'll start. I mean, we do have a number of work groups, I think. One of our work groups on the anthrax, and Drusilla may want to speak to that. I mean, it's a classic example of how we're working to be -- it's interagency, and how we're addressing some of the issues with developing animal models.

DR. BURNS: I'm Drusilla Burns, and we actually have set up animal study working groups that the participants at NIAID and DMID started this, and we participate and CDC has participated, and we have actually weekly phone calls, and I think it has been a very synergistic interaction because everybody knows what's going on, what needs to be done, and everybody is working together. It's one of the most rewarding groups I've ever been on.

CHAIRPERSON ROYAL: Yes, Dr. Hewlett.

DR. HEWLETT: I think as Harry just

alluded to, you seem to be operating more and more like an academic institution. You have trainees. You have core facilities. You have people that are writing grants, and I wonder. Some of you like Dr. Carbone came from academic institutions, but I know for a fact that a lot of people have been at the FDA for a long time and didn't go through that experience, let's call it.

Grant writing is not intuitively obvious, and we spend a lot of time at our institution working with the faculty and enabling them to do this process better, and I wonder if that's something that you've thought about or now that you're becoming dependent on those types of funds.

DR. CARBONE: We are very fortunate to be next to our sister agency, NIH, and they have an excellent grant writing course, which we encourage our junior people to take.

Actually, fortunately the group is small enough that with the division directors and other people's help we actually have a pretty good mentoring program we've actually received and commented on. But one of the things, there are a bunch of town hall meetings that I hold with staff, town hall, how to get

promoted, town hall, and somewhere either on my list or I don't think I've done it yet is town hall meetings or regular meetings on how to write grants and how to approach grants.

You raise a very important issue, nd it is a time sync and it needs to be done well, but in part what we're really talking about is communicating effectively in writing and particularly communicating to a non-self audience, and that's a skill we need to learn better, whether or not we write grants.

And in part some of the efforts to rewrite the summaries to plain language them and make them relevance clearer was as much, I think, for staff education as it was for the end effect because between myself and the ADRs, we went back and forth on edition after edition to try and get those in shape.

So it is something we attend to, and we need to attend more to.

DR. WALKER: I've seen these grant proposals come across through my office. Some people have been doing this type of thing for a long time and they have nor problem, but just recently, for example, we got one young investigator who is very frustrated in getting outside grants, and so I talked to his lab

chief, and what we're going to do this summer because he[s going to submit something in September is a number of us are going to work with him, you know, sort of team up with him, and try to give him that little extra mentoring that will helpfully help put it in plain language, and so forth.

But that is a problem. I'm glad you identified it.

DR. BRENNAN: I think, Eric, you're right. It's a good problem. It is sort of good and bad. You know, we can't write our RO-1s. So you know, we don't have to write that kind of extensive. As you saw, a lot of the external funds in the beginning are within the agency's NVPO and in DoD. They tend to be smaller, targeted proposals, where we sort of know what they want already, and they're a little bit easier to write.

One of the strategies we've been taking, it's actually based on a comment and idea that Dr. Baylor had about a year and a half ago, was to try to become a center of excellence for some of the things that we're really good at, like assay development and things. So I think one of the strategies we're thinking about and because also a lot of these smaller

grants are like one year, maybe two years so that we don't have multi-year grants, is to get more multi-year grants, and where we have a combined program project-like grant. The cell substrates is an example of that, and we're now pursuing a new one with NIAID based on our scientists, and we actually have 12 proposals in this program project grant from 12 individual PIs that are focused on us developing potency assays and related to serological correlates and also animal models and related to the animal rule, things that would really fit into that critical path to move basic research into the -- a product from basic research into the clinical trial, something that's a little further along where decisions can be made, which product to go forward.

And so I think that's a focus we're trying to take, and I think maybe this addresses some of Pam's issues before. What are some of the new strategies we can take to get multi-year funding.

Now, the down side of that is it's still external funds. You know, it doesn't bring us FTEs. So we still have to focus on the fact that if we get a bunch of money, it's still going to be for whatever that proposal's goals were. So it brings it out of

our hands a little bit.

So we do have to have balance that we have to work with.

DR. CARBONE: I just want to make an editorial comment in that light of new strategies. One of the things that's very difficult for us is because the concept of product development specifically lies usually within industry or in the FDA, those things that you really need to get a product through. We are faced repeatedly with grant calls and grant reviews where that whole part of the equation is left out, even in organizations that say the goal of this call is to have products to people.

And in fact, we have been asked. I can think of several agencies and outside partners where I've been asked or our people have been asked to review proposals, and the questions have been, you know, will this make it to a product; is this what we need to have, a product, and the answer is almost uniformly about 75 percent of the time no.

And in terms of getting sort of the expertise and the center of excellence, it's a bit frustrating to see proposals coming out repeatedly with this intent, and yet they don't have the

expertise they really need to get done what they really want done. And the critical path is helping, but there's just not enough information out there. There's not enough recognition of this need so that where our expertise could help, we're often bypassed, if you will because no one understands that this is critical to what they're trying to do.

In fact, we have chased groups down. I personally have heard talks and gone to talk to people and say, "We can help you with this call." I mean, we won't review their grants and say up or down, but we actually have in one case it ended up being an open meeting where we gave a CBER 101 to the evaluation staff to get them a little education about what they really need to be looking for if they really wanted a product at the end of this grant call. So we try.

CHAIRPERSON ROYAL: I have a question. You mentioned earlier, actually the very first speaker, Dr. Goodman mentioned the fact that filling some of these niche areas tend to bring along with them revenue that supports the research, benefits the center.

At the same time the work that continues on is obviously filling the niche as well and maybe

might not attract a high level of funds. Is it acceptable for consultants to be engaged to work with Division Directors, labs to generate approaches that might be revenue generating and that might benefit a division or the entre program?

DR. CARBONE: It's very tricky with the federal system because, for example, the question was asked about charging for samples. In fact, in my understanding -- and I don't want to cut things off before they start -- but my understanding is from discussions with some of the experts in the law on this is that we're actually not allowed to charge in many cases, and even if we did, it must go to a general fund.

So I think there could be --

CHAIRPERSON ROYAL: That's a start.

DR. CARBONE: Exactly.

CHAIRPERSON ROYAL: The general fund is a start.

DR. CARBONE: Well, no, no, not our general fund. A general fund, meaning the Treasury.

(Laughter.)

CHAIRPERSON ROYAL: Right.

DR. CARBONE: Not our general fund, a

general fund.

And we have to very, very careful and appropriate about anything that is viewed as a money making enterprise because our job is regulation. I think we're talking about should we be getting outside funds, et cetera. I honestly thing a bigger fear of ours is that some day somebody will write a line in the budget that says it is now deemed that the FDA does not need to do research. No money will go to research, period. I think that's the biggest concern we have.

When I arrived here ten years ago, in fact, I was instructed never to mention the word "research" and FDA in the same sentence, which is why I was delighted that the critical path came from the Office of the Commissioner, which essentially opened that door once again.

So I think part of what we're asking for help in the committee is to make sure that -- Jesse and I have described it to each other as this. Our research must be targeted and high quality and valuable. If it is, we may have some hope of getting it supported. If it isn't targeted, of high quality and valuable, we have no hope of getting it supported.

That's kind of where we are.

DR. BAYLOR: Although it's an interesting twist because we believe our research is of high quality. Obviously because we're getting external funds at are extremely in excess of what we are getting in appropriations. So it's an interesting twist.

I mean, sure, it's for the most part still government money. The competition is not an RO-1, but at the same time, we are having to compete for those funds. I think the sister agencies believe we are doing quality work. So we're getting that kind of revenue, but we are having difficulties getting the appropriated part.

DR. CARBONE: But we can't lobby by law.

CHAIRPERSON ROYAL: Maybe monies going into the general fund can be rerouted during later budgetary years back.

Sorry. Dr. Tacket, I think, had a question.

DR. TACKET: What is the expectation for the appropriation moving into the future? Is that up or down? I can't remember. That's down.

Is it political? Yeah.

CHAIRPERSON ROYAL: You mentioned earlier the interactions, and I think Dr. Tacket asked about your interacting with other foundations. To what extent are those foundations able to co-fund positions or actually place people in the lab for various periods of time.

DR. CARBONE: They cannot provide us FTEs or support FTEs. They can provide funds for contract researchers, such as our post docs or ICE Fellows, ERD Fellows, and we have successfully worked with foundations to do this.

I don't mean like the NIH foundation. I mean private foundations. We have experienced some difficult in funding flow, which is the most pushed mechanism, which is the CRADA, cooperative research agreement, and we have the CRADA grant, which is a little more like just here's the money; do the work.

The CRADA is designed as you and I are doing the work and you are paying your portion.

We have had it expressed quite clearly from several foundations and other institutions that they do not want to use the CRADA or CRADA grant mechanism, period, end of story. We won't give you money.

We have been working with the Office of Commissioner to talk about other routes and other possibilities and, in part, this is where the FDA foundation discussion arose because that might be one way to work a single pathway that everybody feels comfortable working with, can be sheltered from conflict, et cetera.

But again, we require an active legislation and about seven or eight years to develop, and we need a congressional champion to do that.

Not lobbying. I'm just telling you.

So we have been successful, and in fact, we try and engage the foundations where our missions are clearly, clearly an alignment to do that, and Dr. Goodman himself has been active in doing that. So that's a route we do use.

CHAIRPERSON ROYAL: Yes, Dr. Greenberg.

DR. GREENBERG: So a number of times people have talked about product development and the industrial side of the research that the FDA needs to do. It seems to me it will be that a lot of expertise that would be useful to you exists in industry actually, and it seems to me also that I know of flow from the FDA to industry in personnel. I'm not really

aware of flow the other direction.

Is there any? Does the FDA have any ability to recruit people from industry? Does that happen?

DR. WALKER: I came from a biotech company and Dr. Blake has come. Some people have come from industry. You know, it has gone both ways.

CHAIRPERSON ROYAL: Yes, Dr. McInnes.

DR. McINNES: It strikes me that I think it's the profound commitment of the office of staff to actually conduct of the mission and the high quality with which you do it, is in fact in the absence of appropriate resources is, in fact, part of the problem, and nothing is allowed to fail. Nothing falls through the crack because of the personal commitment and the organizational commitment to what your mission is and your core mission.

In just sort of a fundamental principle of raising children, while you get what you want from them, you don't really have to change the baby.

I speak, you know, with sort of heartfelt respect for your organization, and I recall times from influenza where I swear I think we were going to graze the sheath on the lawn outside the building because we

couldn't even have the money to pay.

And I think, you know, as much as I'd like to be creative and brainstorm about accessing additional resources, but I mean, the core issue is that it does not appear that you're appropriately funded to carry out your mission.

And I think that is the fundamental issue that needs to be on the table, and how to address that is something that we'll have to brainstorm about, but that is a reality.

DR. CARBONE: Yeah. I mean I think just to put this on the table, there is no way that we would ever do anything but our utmost regardless of any funds provided because what we're dealing with are people and their lives. So that's not striking as an option or work stoppages or slow-downs.

However, I would also give the clear message in many cases, for example, in site visits for labs, we get the continual message, "You need funding. You need Funding. You need funding." Somebody needs to tell Dr. Goodman.

I can tell you Dr. Goodman knows. Even Office of the Commissioner understand at some level that this is a problem for the whole agency, and

research being the tail end, is the canary in the mine. For many organizations, the first thing to go when budgets get tight is R&D.

So all I can say is I think the message is well understood within the agency.

DR. BRENNAN: And I think what it is, Pam, is that you don't so much see failures, but what happens is things don move ahead quickly enough. They don't move ahead as best as they could. For instance, we'd like to have a BL-3 facility for tularemia. We can't afford it. We just can't get it, but we could move things faster if we had that BL-2 facility because we have the expertise.

So it's more, I think, as something subtle that you don't see, you know, the facilitation, the acceleration of things happening faster is part of it.

DR. SHAW: Well, if things aren't bad now, I'll give you something that's going to make it a lot worse. I think everybody realizes that we're on sort of the beginning edge of a real boom in new technologies of one sort or another, and I won't even bother to try and list them. You all know a lot about where they are.

And is there any kind of distant early

warning system that you have set up either deliberately or informally to say look at new pre-IND requests, to say, you know, there's a vaccine made this way coming our way? And oh, now there's three of them. We've got a wave here.

Are you doing that sort of thing?

DR. BAYLOR: Yeah, we do that. We do that all the time. I mean, there's a debate on how you respond to this. I mean, we believe that you really need the laboratory based science to really optimally deal with these emerging issues, these emerging technologies, these new, innovative technologies, and others may not believe that's necessary. We do. I mean, this is our history. This is how we facilitate it, product development.

One could ask, well, what would happen. I mean this is sort of in response to your comment, Pam. What would happen?

I mean, we've been down this road before. What would happen if we were not prepared for those? And we're getting to a point where we are less prepared. We are not going to be able to respond as well if we lose this valuable resource, and it's very difficult.

Yes, we are always concerned about that. When I look down the pike, and you and I were in Cleveland. You know, some of the technology that was coming out of there, I'm scratching my head saying, "How are we going to handle that? You know, where are we going to find the staff to be able to deal with that?"

And you know, it's our mandate. We're going to have to figure it out, but without the appropriate resources, I don't know. Maybe that's when it hits the fan, Pam. I don't know, but we have to do it. We're going to have to be able to respond somehow.

DR. CARBONE: What would be helpful to us would be to concretely identify the priority areas that everyone, their expertise on the panel, sees coming down the pike. I mean, because we do have scientists, there's proteomics, nanotechnology.

I mean microarray is almost passe at this point, but I mean there are issues of the data collection, the bioinformatics, the statistical evaluation. So it would actually be quite helpful to us if you could identify what meager resources we manage to scrape together. Where is our best

investment?

For example, we lost a huge proteomics resource when we lost Chip Petricoin. By the offices working together, collaborating with resources that I think we're going to attain from outside the center, plus from some internally, we've managed to cobble together a little critical mass of protein chemistry and proteomics.

In addition, many of our proteomics scientists are protein chemists, left to go to CDER when this split occurred. So we had also another gap to fill, but we've managed to cobble together our little group to start to work on that, and it's starting up as a cost center coordinated group. They all have their product expertise, but the group is a cross-center group.

So other areas that you would think would be high priority, we should invest. That would be great to hear about.

CHAIRPERSON ROYAL: Could you expand on what led to you losing your proteomics expert?

DR. CARBONE: He got an institute. Yeah, I mean, we weren't even talking the competition there.

CHAIRPERSON ROYAL: Well, it sounds like a

number of the issues have been a problem for a while, but would you say that things are operating now the way they were maybe 40 years ago? And if things are different, how are they different?

DR. BAYLOR: Well, when you speak 40 years ago, 40 years ago we had a research program. We had a fairly well funded research program. Forty years ago, we were part of National Institutes of Health. We don't have that resource anymore. We are part of FDA.

And again, we really don't want to digress into budget and things like that here, although it's just here. It's obvious, but our appropriations are different from HHS. We sit in HHS, but our funds come from Agriculture. So we are competing against different things.

And I think until that -- I mean, this is my personal opinion -- until that changes, I think we're always going to be in a very awkward position, and the day that that transition will happen, I think the writing was on the wall when what we used to be under NIAID switched over.

So it's a different time.

CHAIRPERSON ROYAL: The comment has been made that to a large extent your office operates very

similar to what you see with academic institutions. One thing we're seeing is much more interaction between both tech and academic institutions to the point where if I go to an online newspaper and click on an ad that says that the Mayo Clinic knows how to reduce your blood pressure, I end up going to a drug advertisement.

So do you see your regulatory role with respect to academic institutions changing or your regulatory role changing to address that?

DR. CARBONE: Well, you know what makes our life quite difficult is finding unconflicted Advisory Committee members.

Yes, Christine? Trying to find somebody who doesn't have a conflict these days is very difficult because of the blending of these sorts of agencies.

There are cases where we can work with biotech to solve problems and industry. There are cases where we have difficulty. There are cases where we do work because it's absolutely necessary, but then that extracts that individual from any review responsibilities because they no have some kind of direct relationship that involves research funding

with a regulated industry.

So we have a much higher bar when it comes to setting up any kind of a relationship, and we also have to always go back to the core mission, which is to do the regulation, and the need to, quote, make the research funding is an outgrowth of the appropriated funding and a designation of where the appropriated funding goes to.

Any time we start getting too far down and becoming an organization focused solely on bringing money, which is more of the academic model, questions of our core function arise.

The way we've done it is we've done it typically with other agencies even within DHHS that have similar missions, but we never really want to ever be viewed as a money making or how to get funding enterprise because that gets us too far from our mission.

DR. BRENNAN: One area where that has affected us, Dr. Royal, is in travel to universities, for instance, to give presentations on the research. It used to be that our researchers could accept invitations to present their research, which is part of our visibility to the outside world, and now

because so many universities have association with industries that we regulated that we have to now, if we're going to do that, we have to pay from internal funds for that travel. So all those little things add up.

DR. CARBONE: That's the case where having a foundation you could see is very clearly helpful because the funding could be provided to the foundation for travel in a nonconflicted manner, but we don't have that option currently.

CHAIRPERSON ROYAL: I don't entirely understand the difference and how that would work in interacting with the foundation.

DR. CARBONE: Oh, I should say n FDA foundation. Sorry. I wasn't clear. Yeah, an FDA foundation.

CHAIRPERSON ROYAL: And the source of funds for an FDA foundation would be from?

DR. CARBONE: Philanthropy, individual donors. It would be people interested in having -- typically you would think of an organization with a particular disease might donate funds to a foundation. It's an administrative pathway to sort of separate the conflict of the funding. The funds would be all

handled through the foundation.

CHAIRPERSON ROYAL: It's a fine line.

Yes, Dr. McInnes.

DR. McINNES: In terms of making a list about challenges that one sees that would be coming down the park in products, I mean, the one that clearly I think would be a good problem would be looking at sort of pivotal efficacy trials for an HIV vaccine candidate and whether you feel adequately prepared to be dealing with that or there are some gaps there.

And in the malaria question about the plethora of candidates that one is seeing, I know you do have some malaria work, but I'm wondering if you feel that you have adequate strength in this area or if that is an area that you really perhaps need to focus on.

I think it's a very challenging area. I think you've done a lot in addressing the cell substrate adventitious issues, as the cell line issues, cell derived, cell substrate derived products which I think would spin off to the flu vaccine. Do you feel that you have adequate strength there? Do you feel you need additional strength there?

And then -- well, let me start with those.

DR. WALKER: Actually malaria is a good example because we don't actually have in our division work being done on malaria. We're fortunate that we've got one person who has worked on malaria before, Marcella Parra. Also up in the Clinical Division, DVRPA we have Jon Daughterty up there who has worked with malaria before, and so that brings some expertise.

Then Dr. Morris has formed a malaria working group. So other people in FDA who are interested in that at least meet to discuss issues that might relate to malaria.

There is someone in Blood who has worked in malaria before, which is not in our office, and that person has helped us before, but that's the only person who is actually working.

We have talked about trying to get somebody in that should be efficient money-wise, maybe team up with the people in Blood and, you know, help each other out that way, but we don't have the resources for that yet either.

So it's a problem. Yet we estimate there may be up to a dozen new malaria submissions coming in

the next year or so. It's tough.

DR. WEIR: The two that I think you mentioned, HIV, cell substrates, I guess I'm always reluctant to say we have enough of anything, but in those two areas, they have been priorities for a long time, and we do have quite a few people that focus on HIV issues related to HIV and vaccine development as well as cell substrate issues, and again, back to what I mentioned earlier in the cell substrate area. That actually takes advantage of a wide range of expertises.

And so for those two areas, yes, we're pretty well staffed for right now, and again, a part of that is because it has been a priority for a while.

DR. CARBONE: Keep in mind that statement is made at the point of view of the FDA because the staff, when he says "well staffed," there are laboratories in the organization --

DR. WEIR: Yes, it is all relative.

DR. CARBONE: -- that are as big as that entire division. So whenever we have more than one or two people who can handle something, that is viewed as well staffed.

DR. McINNES: You can imagine the

onslaught that you know very well that will come with pandemic flu, and there will be in terms of trying to drive the cell based product, again, which we've seen huge investment in, both in the private sector plus in the public sector.

And I can imagine the pressure to license those products will particularly be relentless, and so, you know, I'm sort of thinking about it as having base knowledge that is going to be able to be applied to those particular situations.

I know you think about this all the time, but I'm just interested in thinking about two specifically.

DR. BAYLOR: And that's where we have to sometimes pull. I mean, the flu is a good example. I mean, sure, we were very fortunate to get the supplemental, but remember the supplemental, let's just take, for example, the supplementals start today. So I go out and hire new FTEs. Those FTEs are not trained. So what I'm using are people who are already in place, who are already trained, and I'm pulling people who have the flexibility, as I jokingly said before. You review the virus. Here's another one.

And those are the people who are at the

front line, and that's how we are having to handle this.

Now, yes, we are fortunate with the flu supplemental. If we get this onslaught of malaria application, and it's coming, I don't really foresee the department saying, "Oh, now we have to have a malaria initiative," but maybe it will.

But we are still going to have to be prepared, and what we will have to do is take experts from other areas just as Dick has indicated, with Sheldon from the TB lab, and you know, we're going to have to piece this together. But we have to respond.

CHAIRPERSON ROYAL: Any other questions?

If there are no questions at this point, we'll move on.

DR. GREENBERG: I did.

CHAIRPERSON ROYAL: Oh, sorry.

DR. GREENBERG: Norman, what happens if you can't respond? I mean, I understand the feeling and I respect deeply that feeling that you have to respond, and I agree from the level of the country you have to respond, but sometimes there's 24 hours a day, and if there's ten malaria vaccines, I mean -- and the other thing is not everybody is fungible. So

a perfect response would not be taking -- you know, having nobody who knows anything about malaria dealing with 12 vaccines.

So I think that's what Pamela was getting at, is we know you will get through it because you always have, but you want to respond optimally, I guess is the --

DR. BAYLOR: Right, and we very much want to respond optimally, and I think we have all discussed internally what will happen that day that we can't respond. I mean, I guess theoretically it could happen, and you know what that means. It really has a huge impact on the public health in this country.

CHAIRPERSON ROYAL: Okay. If there are no other questions, we'll move on to the open public hearing portion of the agenda.

MS. WALSH: As part of the FDA Advisory Committee procedure, we are required to hold an open public hearing for those members of the public who are not on the agenda and would like to make a statement concerning matters pending before the committee. Is there anyone in the room who would like to make a statement before the committee?

(No response.)

MS. WALSH: Okay.

CHAIRPERSON ROYAL: Thank you very much. At this point we will break for lunch and return at 2:00 p.m. for the closed committee discussion.

We can come back in an hour.

(Whereupon, at 12:47 p.m., the hearing in the above-entitled matter was recessed for lunch, to reconvene at 2:00 p.m., in closed session.)

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