UNITED STATES FOOD AND DRUG ADMINISTRATION

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SCIENCE BOARD ADVISORY COMMITTEE MEETING

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March 31, 2006

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5630 Fishers Lane, Room 1066
Rockville, Maryland.
8:00 a.m.

DR. KENNETH I. SHINE, M.D., Chairman, presiding.

PRESENT:

KENNETH I. SHINE, M.D.The University of Texas System

GAIL H. CASSELL, Ph.D.Eli Lilly and Company

SUSAN KAY HARLANDER, Ph.D.BiOrational Consultants, Inc.

LONNIE KAY, DVM, MPAMichigan State University

CATO T. LAURENCIN, MD, Ph.D.The University of Virginia

BARBARA J. McNEIL, MD, Ph.D.Harvard Medical School

JAN N. JOHANNESSEN, Ph.D.

DAVID R. PARKINSON, M.D.Biogen Idec

XAVIER PI-SUNYER, MD, MPHSt. Lukes Roosevelt Hospital Center

ALLEN D. ROSES, M.D.GlaxoSmithKline

KATHERINE M.J. SWANSON, Ph.D.Ecolab, Inc.

JOHN A. THOMAS, Ph.D.

A G E N D A

P R O C E E D I N G S

(8:58:40 a.m.)

DR. SHINE: I'm Ken Shine, currently Chair of the Scientific Advisory Board, and it's my privilege to welcome you to this meeting. We are privileged to have two new members of the Scientific Advisory Board with us. Dr. Lonnie King is Dean of the Michigan State University College of Veterinary Medicine, and Mr. David Parkinson is Vice President for Oncology and Therapeutics at AMGEN and they're both sitting at the end of the table. I was always struck by the fact that whenever as a professor I opened a class, there were always those people whose chose to sit in the back of the room. But in any case, welcome. We're delighted to have you.

Before we begin our meeting, I would like to take a moment to go around and have them introduce themselves, just with a sentence or two in terms of their background and interest. This is partially as a way of reminding all of us what we do, and on the other hand, to introduce people to Drs. King and Parkinson. So perhaps I should start out by saying

I'm a cardiologist interested in issues related to cardiovascular drugs, and also very much interested in questions related to patient safety and the safety of drugs. Cato.

DR. LAURENCIN: Good morning. I'm Cato Laurencin. I'm a Lillian Pratt Professor and Chairman of Orthopedic Surgery at the University of Virginia. I'm also a Professor of Biomedical Engineering and Chemical Engineering at the University of Virginia with interest areas in medicine, orthopedic surgery, and also biomedical and chemical engineering.

DR. SWANSON: I'm Katie Swanson, Vice President of Food Safety at Ecolab. I'm a Food Microbiologist and interested in food safety and food science, and various aspects of the food supply.

DR. PI-SUNYER: I'm Xavier Pi-Sunyer. I'm an endocrinologist. I'm Professor of Medicine at Columbia University, and I'm interested in diabetes, obesity and nutrition in relation to medicine.

DR. HARLANDER: My name is Susan Harlander. I have my own consulting company called BIOrational Consultants. My training is in food

microbiology and biotechnology, and I'm involved in risk assessment and developing software programs in the event of a food safety or food bioterrorism event.

DR. ROSES: I'm Allen Roses. I'm Senior Vice President for Genetics Research in GlaxoSmithKline. I'm a trained neurologist and geneticist, and my interests are in genetics of human diseases and pharmacogenetics with specialty in drug development and surveillance.

DR. McNEIL: I'm Barbara McNeil. I'm head of the Department of Health Policy at Harvard Medical School. I'm also a Nuclear Medicine Physician at the Brigham & Women's Hospital. I spend a lot of time on research related to quality of care and technology assessment in medicine.

DR. KING: Good morning again. I'm Lonnie King, Dean of the College of Veterinary Medicine at Michigan State University. My interests are epidemiology, food safety, and zoologic diseases, and prior to being at Michigan State University, I was with the USDA for 19 years, and also served as the Administrator of APHIS, Animal Plant Health Inspection

Service.

DR. PARKINSON: I'm David Parkinson. My background is medical oncology. My area of interest is therapeutics development in cancer, and I've just recently taken a position as Senior Vice President responsible for oncology research and development at Biogen Idec.

DR. SHINE: Thank you very much. We will be meeting a number of people at the other end of the table in the course of the presentations today, so I think we won't have everyone introduce themselves at this time.

It's now my privilege to introduce our Commissioner. Before he can speak, we have to waive things, so Jan Johannessen will waiver.

DR. JOHANNESSEN: Thank you. Good morning. The following announcement addresses the issue of conflict of interest with respect to this meeting, and is made part of the public record to preclude even the appearance of such at the meeting. The Food and Drug Administration has prepared general matters waivers for Drs. Shine, Cassellarlander, King,

Laurencin, McNeil, Parkinson, Pi-Sunyer, Roses and Swanson. A copy of the waiver statements may be obtained by submitting a written request to our Freedom of Information Office. The waivers permit them to participate in the Committee's discussion of a review of FDA science programs, updates on drug safety programs, FDA's response to a science board peer review of the ORA Pesticide Program, planning for the peer review of the CVM NARMS Program, and an overview of the Office of Women's Health.

The topics of today's meeting are of broad applicability and unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. The participating committee members have been screened for their financial interests as they may apply to these general topics at-hand. Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each participant. The FDA acknowledges that there may be potential conflicts of interest, but because of the

general nature of the discussion before the committee, these potential conflicts are mitigated.

We have the open public comment scheduled for 1:00 and we would just remind everyone to turn their microphones on when they speak so we can transcribe this meeting. Thank you.

DR. SHINE: Thank you very much, Jan. Mr. Commissioner.

DR. VON ESCHENBACH: Thank you very much, Mr. Chairman and I welcome Dr. King and Dr. Parkinson. And I, particularly on behalf of the FDA, want to thank each and every one of the members of the Scientific Advisory Board. I don't think anyone cannot be just overwhelmingly impressed as the Chairman went around the room and asked you to introduce yourselves. To listen to your incredible, amazing diversity with regard to your skills, your background, and the tremendous talent that you bring to this board, so we've very, very grateful for your kindness in spending so much of that talent and time and energy in support of the FDA.

I want to talk to you this morning about

what I believe is our shared vision for the FDA, and the FDA going forward from a perspective that we're in the midst right now of our centennial celebration looking back over a hundred years of incredible progress that as you have pointed out have made the FDA the gold standard in the world for assuring the safety and the efficacy of the foods, the drugs, the cosmetics, the devices, the foods that we feed our pets, and 25 percent of everything that we consume in this country. But as we celebrate that very rich past, I think it's critically important that we also take this moment to look ahead, and look ahead at the future, and look at the FDA of the 21st Century.

This, I believe, then begins to frame a very, very important role, and a very, very important responsibility for the board. As we have often pointed out, the success of the FDA has, in fact, been based on the core values that it's placed on the importance of science in guiding its decision and its decision-making process. It is described as a science-based regulatory agency, but I think that as we look at the future of the FDA, we need to look at

that very important role that science is playing and ask the question, as we create the FDA of the 21st century, what will that role of science be? What must that role of science contribute, if FDA is going to continue to be as successful as it has been in the past in regulating the important component of our Gross Domestic Product that we all depend upon. And so I want to talk about the future. I want to talk about the important role of science, and particularly this morning, share with you what we would propose is an opportunity and a vision for the role of the board in helping the FDA with that mission of keeping science at the core of what we do, and what we are responsible for as an agency.

As we look at that future, I'd like to take just a moment to put what I believe is a challenge that's not only facing the FDA, but our entire health and healthcare profession; and, in fact, our entire society. And that is the fact that we are in the midst of unprecedented and profound change. If we look at the progress in the past, we recognize that it has occurred in a context in which historically

changes in medicine have been slow and, perhaps, evolutionary. And I have been pointing out that as we look at our current concepts of what our definitions and understanding of health and disease are, we are placing those in a context that for thousands of years the only way we had of being able to perceive and understand health and disease was from a very macroscopic perspective: what we could learn, and understand, and discover simply using our five senses. And about a hundred years or so ago, we moved from that macroscopic perspective and understanding to a microscopic perspective in which for the first time we could really begin to know and understand things by being able to see the cells that made up a tumor or the organisms that were responsible for an infection. And that transition into the microscopic era was, in fact, a very profound transformation.

Somewhere in the middle of this last century, in the middle of the FDA's hundred years, science began to move into a new era, an era in which it was preoccupied and focused with understanding the very fundamental nature of life. And over the last

half of the 20th century, we have moved from a macroscopic and a microscopic perspective, and perhaps in the past 10 years have crossed the threshold so that now science has provided us the opportunity to understand and perceive disease and our concepts of health not from a macroscopic and a microscopic view, but from a molecular view. And that transition into that molecular perspective, I believe, is even more than a transformation. It is so profound a change that it is really what I would describe as a metamorphosis. It's a change that's so profound and science has created an opportunity, therefore, that's so profound that the future will look no more like the past than a butterfly looks like a caterpillar. It is that significant, and it is that profound, and it is an opportunity and a process of change that will not change one thing, but I believe will change everything.

We have already begun to just get glimpses into what the profound implications are of the kind of progress that's being made in science and technology and how that is influencing not only our understanding

of disease, not only our understanding of the disease processes, but also the understanding of the person and the human being who is susceptible to those diseases. And it's opening up enormous opportunities for us to begin to rethink and re-evaluate how we may, in fact, be able to impact upon those disease processes and those fundamental life processes.

And so, as we have engaged in this process, we have begun to see the fruits of all of this discovery, and all of this scientific progress begin to be able to be translated into interventions that are now beginning to impact on people's lives, and being delivered to patients and to populations in a way that can alter and change disease, and redefine our concepts of health. And those opportunities are occurring across the full spectrum of everything that the FDA is responsible for and regulates within its portfolio, from food to drugs, to biologics, to devices, and even, in fact, on to cosmetics. And so, the FDA of the future is challenged and responsible for beginning to understand and integrate the very fundamental and profound changes and alterations that

are being brought about by this molecular metamorphosis, because, in fact, the FDA sits between the world of discovery and the world of delivery embedded in both, but being, in fact, the bridge that supports the development and the transition of all those new opportunities and promises to the point where they actually become interventions that are applied and delivered to patients and people.

And so, just as science and technology is changing the world of discovery, science and technology is changing the world of development, and the world of delivery, and the FDA is critically positioned and critically responsible for not only being a part of that, but, in fact, being a part of catalyzing and leading that entire transformation. And if the FDA is going to be successful, it must also change. It must begin to look at what our responsibilities and roles must be to be able to adapt to this new reality. Just as science is producing and creating these opportunities for change, science will also illuminate and lead us into what those changes must be. And so, as we have considered FDA a science-

based regulatory agency, I now believe we are also charged with being a science-led regulatory agency. And a science-led regulatory agency that facilitates, and promotes, and helps to lead this transformation.

In order to be able to be successful at being a science-led agency, we need and desperately will continue to depend upon the very important role that this board has played and must need to play in creating and defining the future of the FDA. And so, I would like to begin this morning by presenting and proposing that we take an opportunity to begin to examine and to evaluate what that new role and what those new opportunities might be for the board, and what those new and continuing contributions will mean to the FDA.

Later this morning, just following me, you're going to hear three presentations of a perspective of our scientific portfolio, to begin to frame and define what I believe are some of the opportunities for us to be able to more effectively manage that portfolio. What I would like to propose and look forward to is that we begin to engage the

board in a more active, more proactive way of helping us manage that portfolio. I believe the board has important and essential opportunities in which by both advising, as well as evaluating, and also in addition advocating for the FDA's scientific programs and scientific agenda. We will be able to make that portfolio a much more effective and much more appropriate portfolio of research to be responsive to the challenges that we are facing before us.

FDA science is critical. It is essential if we are, in fact, going to be able to fulfill our responsibilities in the new era of the molecular metamorphosis. But the FDA science must also be unique, and it must also be informed and be immersed in all of those changes and all of that progress that is occurring within the entire world in the entire context of the scientific community. We need to not only be responsive and to be aware of the important dimensions and components of our own internal portfolio to be certain that they are aligned and organized internally so that instead of being compartmentalized and siloed, we, as an agency, have a

coordinated and integrated, and synergistic scientific agenda. But that agenda also needs to be embedded in the opportunities and the interactions that are occurring outside of the FDA, and particularly in other sister organizations and institutions engaged in fundamental research, such as the NIH.

Being able to position and appropriately define the scientific agenda and the scientific portfolio of the FDA in that context will greatly be benefitted by the inputs, the advice, and the direction that the board can provide. You bring, as you expressed in your very introductions, a broad perspective and diverse set of backgrounds and insights, and understanding. You come from a world in which you have an investment and an engagement in the larger scientific agenda, and the larger scientific community. In that context, you become very important parts and pieces of what can be advice and direction with regard to refining, defining, and integrating the FDA's scientific portfolio.

We must address the issues of what makes the FDA scientific portfolio unique, specific, and

adds value to all of the other dimensions and components that are occurring. It is not a portfolio that is without restriction. The responsibilities that we have with regard to stewardship in terms of husbanding the limited resources that we have with which to address all of the diverse responsibilities of the FDA will always continue to put constraints on the extent and the dimension of our scientific portfolio. And so since we recognize its critical importance to the entire whole, and how fundamental it is to the core mission of the FDA, we must also respect the fact that we need to be good stewards of the resources that we have. Our scientific investments have to be carefully defined, and carefully prescribed, and continuously reviewed and evaluated to be certain that we are, in fact, using our resources in the most appropriate way possible.

So in addition to advice, in addition to helping provide direction, we will also continue to look forward to the board providing an opportunity for stewardship, to continue the constant process of evaluation, and being able to be certain that we are,

in fact, meeting our critical responsibilities.

We have new tools that are beginning to be engaged on a broader scale within the entire FDA portfolio. And one of these strategic opportunities that I made a very strong commitment to was the commitment to Critical Path. And so as FDA begins to look at the new tools of science that are emerging from the world of discovery to be applied to the regulatory processes, we will also need to integrate the FDA's research portfolio into those larger strategic objectives across the entire agency, and those that are occurring in partnership with other organizations.

We're on the verge of enormous progress and enormous contributions in the area of science technology and the opportunities to be of service to the health and welfare of the American people, and of the world. FDA must continue to provide the leadership and the standard of excellence that it has in the past, but it can only do it if it's basing its opportunities and its responsibilities on a firm scientific foundation and infrastructure.

I'm committed to constantly and continuously making certain that our scientific portfolio is, in fact, the absolute standard of excellence that you expect and that the world demands, but to do so we need your help. We need to continue to have you actively and proactively engaged in that process. It will be, for us, a continuous evolving experience, and as we go forward, we will learn together how we can continue to refine and enhance that process and that opportunity.

The presentations that you're going to hear and some of the questions that have been posed in terms of the specifics with regards to the opportunities and roles that the board will play will be part of this morning's discussion on helping to refine and define that opportunity, but I leave you with where I began with regard to thanking you for the commitment, thanking you for your willingness to engage in support of the FDA's mission.

I pledge to you, as I have to the entire organization, that as I look forward to the opportunities before me, that the institution will

always be the science-based regulatory agency we have come to be so proud of. But in addition to that, it will also be a science-led agency in which science will illuminate a pathway forward for the FDA of the 21st century. Thank you, Mr. Chairman.

DR. SHINE: Thank you very much, Commissioner. Would you be able to take some questions, comments? I should, perhaps, preface this by emphasizing as I have in the past with the Commissioner that this committee has had the opportunity over the last few years to review the two final proposals for the award program in the FDA, and we look at some seven categories of science. And as one of my colleagues said, sometimes I think I should just flip a coin, the quality of the science and those proposals is extraordinary. And I think the board really appreciates the kind of work that FDA scientists do.

At the same time, I think the emphasis that you've made on relevance to the mission is absolutely key in an environment in which NIH funding is actually negative. We'll have to see what happens

with regard to the changes in the budget, and in which the agency has clearly had to make very difficult and, indeed, painful decisions about how its resources are used. The Science Program has come under enormous pressure, and understanding the relevance of that science to the mission of the agency is absolutely crucial if we are going to convince policymakers and others that those resources, instead of eroding, can, in fact, be not just maintained, but actually expanded so that we take this charge very seriously.

In the course of the discussions, we'll also try to see to what extent our own experience in this regard should provide some guidelines for the other kinds of advisory group activities in the agency when peer review is carried out, because it seems to me that this has to be a process which, if you will, diffuses throughout the scientific agenda of the organization, including the work of the various peer review groups who are looking at particular programs, and particular projects. I think the committee looks forward to taking on this responsibility. Are there comments, questions for the Commissioner? Anybody?

Excuse me. I would like to -- we've gone around and introduced everybody, Gail. Let me welcome Gail Cassell who is Vice President of Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases. And as her title implies, a world-renowned expert in infectious diseases, former president of the American Society of Microbiology and a bunch of other stuff like that. And also, very much in the vanguard of counter-terrorism, particularly bioterrorism. So, Gail, welcome.

DR. CASSELL: That'll teach me to get stuck in traffic, Ken. Thank you for those comments. And I guess it wouldn't be unexpected if my comments are about the budget and looking at the projected increases for FDA for this year just over the past couple of weeks. I'm really depressed at the small increments of increases for all the programs within FDA, and the only thing I can say is that I hope as we have the opportunity to review the role of research and carrying out the FDA's mission, that we will have an opportunity to be able to increase the resources, particularly so that FDA can, in fact, continue to

lead based on science and with the necessary incremental research in order to be able to do that most effectively.

I don't know if you can comment in terms of what your outlook is or prospects in terms of increases towards the future, but clearly, if one looks over the past decade, FDA certainly has lagged the other federal agencies, and as you know, we have, through the National Academies of Scientists just released this report on U.S. Competitiveness in Science and Technology, looking at the really dramatic flattening or decrease in investment in the physical sciences research. And FDA actually kind of falls through the cracks when we talk about physical sciences, as well, and so I think this is an area that we all are going to have to pay a lot of attention to in terms of trying to get increased resources.

DR. VON ESCHENBACH: Thank you. I appreciate the comments very much because it aligns very well with what I would like to reiterate regarding the role of the board going forward from my perspective. And that is, opportunities fall into

three categories, advocacy, stewardship, and advice, an advisory capacity. I think we do need the advocacy, and I think the board can be very helpful in that regard, because it is important to express and communicate to all stakeholders the uniqueness of the FDA's research portfolio, and why it is so critically important that FDA have a major investment in research, and it be a core part of the agency, because many others are often confused that, well, with all the research that's going on everywhere else, like at NIH, why would you need to do research at FDA. So the board can be very helpful because of your understanding of the portfolio and its criticality in advocating and expressing that.

I think you're also right that we will continuously face very, very significant challenges with regard to our resources. But frankly, I believe whether you're in a period of resource constraint or resource abundance, you should be doing the same thing anyway; and that is, being good stewards of the resources. So the board will be very helpful to us in looking at our research portfolio, and continuously

giving us that oversight process that holds us accountable for making sure that we're doing the right things, and doing them in the right way.

And then finally, advice. I would like very much not for the board to be in the process of review, but also in the process of helping us strategically plan for the future in being able to look ahead at what science and technology are determining as important directions and opportunities for the FDA. We need to be ahead of the curve, and not behind the curve. We need to be proactively facilitating this transition from discovery to delivery, and we can only do that if our own science is forward-thinking and not reactive.

DR. CASSELL: Along those lines, I notice that in the appropriations, if I'm not mistaken, that only $15 million were requested for implementation for certain aspects of the Critical Path. And it seems to me that's a very small amount compared to what could be done and should be done with regards to implementation of the Critical Path. Could you comment on that, and maybe how those areas were

chosen?

DR. VON ESCHENBACH: Yes. I think it's important to look at the budget and our allocations from a couple of different perspectives. And I personally am viewing one of the important challenges and opportunities going forward is to take a much different approach to our budget-building process. I think we do have to look at continuously and increasingly advocating, justifying, and building the commitment to the budget and Critical Path, especially from the perspective of our budgetary allocations from Congress, and through the President's budget. So we will continue to move to expanding that part of the process, but I don't think we can totally depend upon that. I think we have to look at other alternative ways of being able to fund research.

One of the important questions the board will help us address in assessing the portfolio is where there's opportunities for us to collaborate and leverage with research that's occurring in other areas so that, for example, by partnerships, or collaborations, or integration with programs in other

areas like the NIH, we have the opportunity to synergize or leverage. And there are components of Critical Path that lend themselves very well to collaborations with, for example, NCI and NHLBI, and other places. And the third thing is other efforts to look at opportunities in the private sector, through CPATH and through the NIH Foundation Biomarker's Initiative, for example, is providing opportunities for resources independent of our own budget.

DR. CASSELL: I know that some of the health research foundations are looking for opportunities in the Critical Path. Does FDA have a foundation like the CDC Foundation and the NIH Foundation, whereby fellowship programs or other opportunities could be taken advantage of by these not-for-profit foundations that wish to contribute to seeing the Critical Path succeed?

DR. VON ESCHENBACH: We have engaged in a relationship with the NIH Foundation, and we also have been engaged in exploring opportunities that may be available through CPATH, another foundation. So we're exploring where these opportunities may lie, so that

appropriately, within all of the appropriate constructs and constraints, that we do this in a way that is appropriate for the FDA. But clearly, we need to look at these other opportunities as ways of being able to provide the infrastructure and the resources to build this program, and we're open to all of that. Dr. Woodcock has been very, very actively engaged in attempting to develop these opportunities, and I'm sure Janet can give you some specifics about that. You want to comment on it now?

DR. WOODCOCK: Well, FDA does not have a foundation of its own, specifically, and that's something we've evaluated intermittently. And perhaps as the board moves forward with its assessment, that could be something you could look at.

In many cases we feel it's best to have the research done in another setting, not all kinds of research, but some of the research, because we will then stand as the evaluators of that research. And we are, with these other independent foundations, and we are acting as advisors who are providing scientific input on design, analysis and so forth, but not

ourselves conducting research that then we would take in and use to create new standards. But there is no doubt, particularly as you said in a fellowship area, we have a critical need for a better way. Since we launched the Critical Path Initiative, people have been beating down our door offering to fund fellowships at the FDA as a way for us to get new scientific talent into the agency and engage in our work, which once you're here you see how interesting it is, I can say myself, that we really need a better way to track fellows and fund the fellows, or allow other parties to fund fellows.

I hear a lot about the drug side of FDA, and I'm wondering if you could comment on the food side. When I first came on the Science Board, there was some suggestion that we might create a Critical Path for the food side of FDA. At least Katie and I have had these discussions as kind of the representatives here of the food side on this board. I wonder if you could comment on where is that in the relative importance of the agency in terms of research, and do you see a potential for Critical Path

development on the food side, as well?

DR. VON ESCHENBACH: I don't think there's any question how extremely important the food side is in the ultimate paradigm that I expressed earlier. If one looks at some of the implications of what I've described as this molecular metamorphosis, one sees not only the traditional things that we're concerned about with regard to using science to understand food safety and that whole dimension. But from the efficacy side of the perspective, and our whole concepts of nutrition, and our whole concepts of how food influences health are moving into an extraordinary area of opportunity that we didn't have access to before because we didn't have that molecular dimension and that molecular perspective. So we need to be even more visionary, I think, with regard to where we're going in the whole area of "food". And the impact that science is going to have in some of those areas, even in terms of our -- for example, one of the things that CFSAN did last week was have a futuring conference that was just extraordinary. But even some of the implications of nanotechnology that

that is going to have across the entire dimension of what's occurring in food, including packaging and monitoring, so I don't think there's any question.

I think one of the points I've emphasized internally is, I think, again, in this molecular perspective, these distinctions, these barriers that we seem to have between concepts of drugs, concepts of biologics, concepts of devices, concepts of food as we look at the traditional FDA portfolio; I think they're blurring. I think they're really become much more integrated than they are separate, and that's another challenge that I would like us to be addressing in terms of our research portfolio, is to begin to see where there are commonalities and similarities between what we have normally thought of as compartments in our portfolio, because I think this research is -- the implications of research span across all these things. I'm looking for more horizontal integration than vertical compartmentalization, so I don't separate food at all. I think it's just integral, and incredibly exciting.

DR. SHINE: Dr. Harlander, you might want

--if you have some specific suggestions or recommendations for the board to consider around how and in what way the role of food and food safety, et cetera, might be emphasized in the course of the Critical Pathway, I think the board would be interested in your thoughts from that point of view. Yes, please.

DR. HARLANDER: I've forgotten exactly when it started, but I'm sure you are aware of the Nanotechnology Initiative that was overseen by OSTPF that began when Jack Gibbons was there, and involved a lot of the agencies -- it was FDA involved in that. And regardless, I guess, whether or not you were, that would seem to be by now an initiative where you should be able to reap a lot of synergy and benefits.

DR. VON ESCHENBACH: Norris has paid very careful and close attention to this and has been leading our whole perspective with regard to FDA's position in nanotechnology and the collaborations that again we've had. And if you'll allow me just to take a moment because it, again, re-emphasizes this point of collaboration and cooperation. So, for example,

when NCI launched its Nanotechnology for Cancer Initiative with about $140 million investment, FDA was a part of that at its very inception, as well as NIST and the Department of Commerce. So this was an area in which FDA was playing a very critically important role in a nanotechnology initiative as a partner, but it was initiated by another agency or another institution, so that's the kind of, again, where I talked about leverage. I think those are where our science can be integrated with the science that others are carrying out. Norris may want to speak to the nanotechnology piece.

DR. ALDERSON: Gail, that's a good question, and we are on the NCET Committee, have been there for some time. We are a voting member of that organization. Under that, as you're probably aware, is the nanotechnology environmental health and safety working group, and I chair that group. Inside the agency, we have what we call the NTIG, and that's the Nanotechnology Interest Group and we meet quarterly. This is made up of people involved in nanotechnology in the respective centers, and this is a means that we

communicate across the centers on what the centers are facing, what type of products they're reviewing, how they're addressing those products. We also started bringing in outside representatives from companies that are developing products to talk about their products and the things they've had to go through in developing the nanotechnology, so we have a lot going on.

Now that doesn't mean that everything is great, because we do have some vulnerabilities in FDA just in the area of cosmetics, for instance, because of the way the law is written, but we'll have to deal with that when it comes. But in saying that, we don't have any indications there are any problems yet, either, so I think we've done well in where we are with nanotechnology. Dr. Von Eschenbach mentioned that INCL Corporation. We're at the table with the scientists up in Frederick,planning what they're doing with those scale materials that they're working on.

DR. VON ESCHENBACH: The question I think suggests, Mr. Chairman, if I might, that the next three presentations as you fill out detail I think

will really help to eliminate some of the issues, but also will surface some additional areas where questions and things to be discussed will surface. So I'll come back and answer questions along with some others, if you think that will be helpful.

DR. SHINE: Hello. Thank you. I would just make two observations. The first is, and the nanotechnology discussion highlights it, and that is on the one hand it's clear that one does want to take advantage of research in other settings. On the other hand, a science-based agency, it seems to me, has to do science. And the question of how much, where, and so forth is a challenge, but I don't believe that we can totally rely on other settings in order to generate the science that is required. And I think part of our charge as we go forward with this initiative will be to try to find some ways to provide some guidance as to the criteria by which that might be done.

And the other observation is I enjoyed your historical description of the evolution of science. I would argue that we're now in a new phase.

I think the last part of the 20th century was, in fact, a period of enormous reductionism, and that we're now in the series now of, to use your term, of integration; that is, whether you talk about proteomics, whether you talk about physiology, many medical schools in this country did away with their Departments of Physiology because they felt all of the science was going to be in molecular biology.

I think we're now seeing the re-emergence of systems biology, of the attempt to integrate, which is entirely consistent with your theme of moving from science to products to benefit people. But again, emphasizes that we have to think ahead in terms of not just how we apply the molecular biology of the past and present, but also how we apply the systems biology of the future, and I think that will be a major challenge as we go forward. Thank you very much, Mr. Commissioner.

DR. SHINE: We'll now move to our agenda and discuss this major project that we'd like to undertake. We're going to initially hear from Janet Woodcock, and then Norris Alderson and Theresa Mullin

are going to follow, and then have a discussion. Dr. Woodcock.

DR. WOODCOCK: Good morning.

DR. SHINE: Good morning.

DR. WOODCOCK: As you've heard, we are hoping to have the Science Board conduct an overview of FDA research with several goals as are written in the handout, and I'd just like to sort of go over the broad picture of this. As you know, FDA's mission is to protect and promote the public health with respect to the products we regulate, and that means we have to make judgments and establish standards for safety, effectiveness, quality, hundreds of standards. And our activities in this area are based on scientific data and assessments.

There is always a degree of uncertainty about any judgment we make, whether it be for the safety for the appropriate level of something in a product that is permitted with respect to effectiveness. There's always a great deal of uncertainty, and this is what leads to all the controversies, of course, about FDA regulation, about

products and so forth.

The scientific research that we need is research that helps decrease uncertainty in our predictions in a wide variety of areas. And I can't stress how broad the areas are of scientific endeavor that we need to bring to bear every day on our judgments, and standards, and our predictions. For example, we need science that helps us develop panels that are used to standardize assays that we use to check for the presence of disease. We develop reference standards, for example, for the West Nile virus in blood, reference panels that industry would use to standardize their assays against. Okay, that's one area of science, a very complicated area.

On the other hand, we have to bring in the science of the behavior of consumers in response to health and nutrition information. It is extraordinarily important social science to us in how we purvey information that actually affects the behavior of consumers and patients, and actually health professionals around regulated products. And sometimes we get that wrong, that prediction, and

people behave in ways we did not predict. All right. And that affects the safety and effectiveness of those products. We need much better expertise and understanding in the social sciences and prediction of human behavior around information. If we want to keep our population healthy, people are mentioning food and nutrition is a critical issue, is how to properly convey information to people in a way that will be meaningful to them.

On the other hand, we have to use science to predict how products are going to perform in the clinic based on evaluation in clinical trials, and somewhat artificial situations. We need to be able to extrapolate from those trials of devices and biologics, and drugs into medical practice and say we believe based on this information, this trial design, this statistical analysis, these endpoints that we have observed in the trials, these monitoring measures that, in fact, the product will perform in a manner that's safe and effective in the hands of the healthcare system. And as we put in our Critical Path paper, our predictive and evaluative science there is

lagging behind, and we really need to improve it.

We need to have science across a huge range of products that helps us predict the consequences of molecules or substances that may be found in small quantities, whether it's animal feed, whether it's foods, whether it's drugs, we're constantly having to make assessments about what are acceptable levels of various substances, and that brings in the entire area of toxicology and predictive toxicology, and understanding the consequences of low levels of substances.

We need, and I know Gail will resonate to this, we need methods to help us with analysis of highly complex data sets. This new synthetic science that Ken was talking about is currently generating data of a magnitude, biological data of a magnitude we really never experienced before, and how to make sense of that, and reduce it to something that we can actually make regulatory decisions off of is a huge bioinformatics and statistical problem that we're going to have to get a handle on in the years to come. And these are wonderful challenges because after all,

this is the advancement of science, and this is how we can actually do our mission better, and protect people better, and promote the public health. However, we're going to have to have access to the science because there's considerable uncertainty around all these questions. And these are only just a few examples. There are hundreds of examples of different types of science, material science, physical sciences, microbiology and so forth.

Now our job at FDA is not to eliminate uncertainty. People are often unclear about that. Our job is to reduce uncertainty to a level that will allow us to make decisions confidently, and support those decisions, and give the public confidence in those decisions, so we need an amount of science that gives us enough confidence that we can move forward in any given area and make decisions.

Now in some of these areas of science, as we already talked about, the research to answer these questions is going on somewhere out in the world, and research will emerge from the NIH, from Department of Defense research, from some research somewhere that's

going on. But for many of the questions I mentioned, and many other questions that exist for FDA, there are very few entities either positioned or interested in carrying out this type of research. And, therefore, if FDA doesn't carry out research to answer these questions, it's not going to happen anywhere else, and we're going to remain with this level of uncertainty that we have, and this has several consequences.

Number one, it impedes innovation, because if we can't provide guidelines to people where they're developing new kinds of foods or ways of processing food, or whether they're developing new medical products, if we can't tell them what the path forward is to develop and assess those innovations, they'll go somewhere else and put their money into something else, because if there's too much regulatory uncertainty because of the scientific uncertainty, then it's not going to happen, and that's one consequence.

Another area on the marketing side, consequences uncertainty, we have great difficulty ascertaining out in the market what's going on, what

the problems are, what the risks are in some cases.

Now as you can see, this challenge is very serious to us because of the broad range of science involved. We are not just talking about one branch of science. We are talking all the way from medicine to consumer behavior, to material science. And we must have expertise in all of these areas, in addition to all the emerging sciences, the proteomics, the genomics, many of the new sciences that are coming forward. So we have, as Dr. Von Eschenbach recalled, we have a portfolio problem. We really need to figure out with our limited resources where are we doing the unique research. We're the ones who are going to do this research, or we're the ones who have to spearhead this research or it's not going to get done. And, therefore, our regulatory mission will be impeded and the public will suffer either from lack of access to innovative products, or from problems related to all the uncertainty around the evaluation.

Now the Critical Path Initiative was partly a response to this, and it is an attempt to bring in a lot of partners and work in these areas of

research and partner with others who share common interests in getting some of this work done. However, I don't think that is the whole response. As was already said, we have to have science here at the agency in order to partner with others. We have to be at the scientific table. We can't just be passive recipients, especially in many of these areas where our questions are very specialized to the FDA, where expertise does not really reside out there about what the very specific problems are that must be addressed for FDA to conduct its mission. So some of the questions we really have - we've struggled with this, obviously, for many years - where should we put our scarce research resources? Each center in the FDA, each group that conducts research has a fairly rigorous process they go through to figure out and triage and prioritize how they're going to spend their research dollars. Are we doing the best we can on that? How can we match the investment versus need, is a very good question portfolio-wise across the agency. Are we leveraging the best we can with the outside partners?

As I said, the problem with this is that we cannot do it in a vacuum. We have to put resources against partnerships for them to function. And we've already learned this in the Critical Path, which is going quite well, but we have very limited resources for that, and it's partly limited by the amount of scientific resources that FDA can put against these partnerships to help move them forward. And it's becoming very clear, even the Critical Path, these are not going to move forward properly and quickly unless FDA puts its scientists at the table, too, and helps move these things along, so that's another question, so we're asking you to take a look at our portfolios. We have a charge here that we want to discuss, a draft charge about the process we're carrying out.

We'd like to know about the research we're doing and what you think of it, and also, what we're not doing. I, personally, am still very concerned that we do not have enough strength in the social sciences area, and increasingly with the media and the flood of information out to patients, and to consumers that we need the expertise to understand the

consequences of that, and the consequences of our labels and our communications. So we would like to know, have an evaluation of what we're doing. We'd also like to have an evaluation of what we're not doing, and what you think the gaps might be in our research efforts that we actually need to fill. So with that, I will turn it over to the next speaker. Thank you.

DR. SHINE: Before you go, Janet, a couple of other comments that I would be interested in your thoughts about. I think you stated some of the major objectives extremely well, including the importance in terms of help with the predictive process in terms of what's happening. I wouldn't want to ignore the notion that you want this done by very good scientists; and, therefore, have to create an environment in which scientists both are respected and supported, and have a sense that they are, in fact, contributing in a way that gives them substantial satisfaction. And a corollary to that is, one of the developments in science is the multi-disciplinary nature of it. Again, I think that's a major 21st

century development that NIH is struggling with in terms of the NIH roadmap which, in fact, does emphasize some of these issues. That means critical masses of people, so I would not want us, as we look at the portfolio, if you will, to ignore the notion that we also have to figure out a way to make sure that fits with an environment in which scientists have both the resources and the stimulation and so forth so that very good people can help do a number of these things.

DR. WOODCOCK: Right. Well, I guess you'll forgive me. I find the environment at FDA so scientifically stimulating, I think once you get inside here, you cannot believe the kind of scientific questions and issues that arise.

I also would like to point out to the board that our reviewers are also scientists, and that should not be neglected. It's most important that our review staff be engaged scientifically, not just reviewing the next application after the next application, but that they have the scientific opportunities, as well, and that there's a dynamic

interchange between the staff engaged in research and the staff engaged in review activities.

DR. VON ESCHENBACH: Yes. Mr. Chair, I'd just like to add another dimension to your important observation and comment. We couldn't agree with you more about the need for being able to bring our scientific community in a way that not only creates critical mass, but facilitates dynamic interactions. And one of the opportunities that I see we need to focus very heavily on is the whole opportunity that's being presented by our consolidation at White Oak, and so we're really looking at that campus as an opportunity for much tighter integration and interaction among the scientists of FDA. And as Janet pointed out, that goes far beyond just the scientists who are in the laboratory. That's scientists across the entire dimension.

Now there's some downsides to that because, for example, CBER has been on the NIH campus, has a lot of relationships that exist there, and we're making certain that we're not detaching ourselves from our relationship with the other parts and pieces of

the scientific community, but we are addressing your important observation of how do we get not just critical mass, but critical integration and interaction among our scientific community.

DR. SHINE: Thank you very much, Dr. Woodcock. I agree with your assessment of the exciting environment. I guess part of the reason I wanted to make the statement was that as the science board goes forward looking at this notion of how the science is driven, if you will, that we can't do that without paying a lot of attention to the people who do science, and the environment in which they're working. Any other comments or questions for Dr. Woodcock?

DR. CASSELL: Janet, I've just been sitting here thinking that I read recently, as many people have, in the news that the FDA oversees about a fourth of the U.S. economy, and yet it's asked to do that with only a little over 1-1/2 billion dollars of taxpayer monies. And out of that, how much of that would be devoted to this research that's seen as so critical to the regulatory role?

DR. WOODCOCK: It's a relatively small

amount. Obviously, we have major enforcement and compliance activities. We have to make sure that everything coming across our borders, for example, the foods that come in, and the medicines and so forth meet our requirements, so we have a major regulatory oversight role in this country that we have to put resources against. We also regulate manufacturing of all these products, and oversee production of the foods and the drugs and devices and so forth. So we'll be providing to the board actual data, and probably can discuss this at further meetings, a breakdown of the actual resources dedicated to scientific research activities, either laboratory or other research, but it's a relatively small proportion of the budget.

DR. VON ESCHENBACH: Earlier in the week I presented exactly that information to Senator Cochran, Chairman of the Appropriations Committee. And Norris can provide a breakdown of that for you, our research investment across all of the portfolio. We've looked at that.

DR. SHINE: So let's do a segue way to

Norris and then we can continue the discussion. Dr. Alderson.

DR. ALDERSON: Let me try to answer your question, Gail, and give you a number that's pretty close, as I recall, what Dr. Von Eschenbach has. And I can provide the board the breakdown by center on this, too. The number is around $140 million. That includes operating and FTE cost. It does not include facility cost, so that's -- and last night talking to some of the senior scientists who were with us last night at dinner, when they saw those numbers, because I did feed that back to them when I put it together, they said that's too high, but that's the best number we have today.

DR. WOODCOCK: Norris, is that testing, does that include the testing labs?

DR. ALDERSON: No, it does not include our testing laboratories. That's strictly our research programs, and the laboratory cost, and it does include about $3 million of the social science work that we do, also. My time this morning is to bring to your attention some of these infrastructure issues that I

think you should be aware of as you frame the science review that we want you to move forward on. And I have one slide, and I'll be using that for all of my comments.

This slide gives you the eight organizations within FDA that do some type of research, and that varies from laboratory, particularly in the product centers, and ORA, as well as NCTR. And the Office of the Commissioner, you say what in the world do they do? Well, there's a lot of social science work that comes out of the Office of the Commissioner.

In addition, the largest extramural program that we have, and that's the orphan products program, is $14 million, and that is strictly a grant program. In addition, you're going to hear this afternoon from Dr. Uhl on Women's Health, they have an extramural program, as well, in Women's Health issues. The other centers also, depending on their budgets, have an extramural program, and that varies depending on which year you're talking about and what the budget situation is.

Usually, when we have an excess, if we can call it that, most of the centers will have extramural programs. But as the budget changes, that's normally the first thing to go, is that extramural program. But in all these centers and all these organizations in FDA, they all are involved in some type of research program, whether it's laboratory or social sciences. Some all of it, some have intramural, some have extramural.

Janet did a very good explanation of the scope of that, and it varies, as she said, from laboratory to social sciences, and between that you'll find statistical issues that our statisticians, particularly in the products centers get involved in looking at, particularly, for instance, are there new ways to evaluate clinical studies. So it's unbelievably broad the areas that we get involved in.

Dr. Von Eschenbach mentioned consolidation of facilities. Last November we met out there at the new White Oak facility for you to get a briefing on the CDER research programs. Well, what you saw at that facility will be completed in 2011, so that's

where we are with the consolidation. Once that is completed, you will have the CDER, CDRH, and CBER all located at White Oak. Tremendous opportunity at this time to look at synergy across the agency in terms of its science programs. The White Oak offers opportunities we've never had before, particularly for those centers at that location. CVM, CFSAN are still outside the White Oak, and they will not be moving there in terms of their research facilities. CFSAN still has four research locations, two of them here in the Maryland area, one in Mobile, Alabama, and one in Chicago, so in the foods arena it's still dispersed, and that is a consideration in terms of your review of the science programs. But with this consolidation, it's an opportunity to look at how can we integrate the science vision, as Dr. Von Eschenbach pointed to this morning, across the entire agency?

I have to tell you when you look at these now, particularly the product centers, they're stovepipes. Their programs are related to their research needs. There is very little communication across the centers. However, I think you will find

when you look, there is not a lot of duplication either. The specific needs of the centers are what they address. They are managed differently within their respective centers. When you look, you will see some of the centers have their research organizations as a separate organization within their center. Others have integration between their review scientists and the research scientists. Some have both, so you're going to find a very diverse means of the way the research programs are managed, and you need to take a look at that as you look at the science of the agency.

All of the agency's programs exist because they get outside resources for their operating dollars. And when you go look at each of the centers, they have extensive programs of bringing dollars in, and there is a lot of those opportunities, I have to tell you. It takes a lot of work to make that happen through cooperative research and development agreements, through partnering arrangements, grant collaborations. We can't, on our own, apply for a grant as a PI to either NIH or USDA.

In the past, we've been able to be a collaborator on a grant, and if a grant is awarded, we get the money to come to us through what we call a creative grant. In the last few weeks, some of that is now appearing to be in jeopardy, so it takes a lot of continual work. I hate to say begging, but that's what we have to do sometimes to find a way to bring the dollars into FDA. There are not many legal avenues to make that happen.

DR. SHINE: Dr. Norris, in the $140 million figure that you cited, does that include money that is research from outside sources?

DR. ALDERSON: No, that's using -- we're referring to appropriated dollars.

DR. SHINE: That's only appropriated money. Do you know what the magnitude of the research effort is?

DR. ALDERSON: Dr. Shine, I can't give you even an estimate of that. It varies by center. For instance, CBER I would tell you is probably our highest in terms of outside funding. And I think Kathy would agree with me when I say this, that a lot

of that relates to their being at NIH.

DR. SHINE: Do you want to say something, Jesse, on this?

DR. GOODMAN: Well, we have a number of areas where we've worked to have cooperative, very targeted agreements with NIH, for example, in cell substrates for vaccines. And I think that's a really nice example of how the kind of thing where Janet said where, in a sense, we have unique knowledge, know what the questions are, nobody else in the world is going to do this, and it really ties into NIH's efforts to better prepare us for emerging infectious diseases, bioterrorism, et cetera. So that's an example of a large partnership with NIH that helps support us.

I would say, just to give the committee perspective; but, again, like Andy said, I think it's important that in looking at the resources, that's a more detailed thing that would require more interaction with FDA's leadership, but I would say understand that FDA's budget was very high proportion of personnel, and that when you hear these numbers, that's mostly what's reflected there. For example, in

our center, there is an extraordinarily small amount of operating money that actually can be devoted to research, so some of this, both us, the leadership of the center and our investigators, and I know our colleagues in CDER in the monoclonal and therapeutic protein areas have similar issues, that there's a necessity to seek partnerships and go outside to even virtually do anything, so that while we can support the personnel, the amount of discretionary funds, as our personnel keeps eating up more of our budget, are very small from intramural sources.

DR. ALDERSON: So at this point in time I think, as Dr. Von Eschenbach pointed out this morning, we are at a point in history of FDA, particularly when you consider the consolidation at White Oak and other issues within the agency, that it's the time to look at how can we look for the means to horizontally integrate across the agency our science needs, particularly for the future. And when you look at the new technologies, and Gail mentioned this morning nano - well, how do we prepare for that in the environment we work in? And we need your advice and counsel on

that issue, particularly, but it's an opportunity to look for duplication across the agency. But, likewise, it's an opportunity to look at how can we increase our leveraging capabilities with other organizations to meet the needs we're talking about.

I'll stop there, and I think I've covered the points I wanted to cover, and I'll answer any questions, Ken.

DR. SHINE: Yes, Allen. Dr. Roses.

DR. ROSES: I was very, very impressed with the Critical Path opportunities list that was just released. And what it's done is it's put some granularity in 76 different categories of things that would be considered critical. And the opportunity for getting the best and the brightest in each of those different disciplines together with the FDA might be served by having focused consortia that consists of those partners, be they government, be they academic, or be they industrial, who have that expertise and can transfer it to FDA scientists in that kind of context. And it would be very useful, I believe, for the FDA to consider how to extend and improve the input to the

scientists within FDA by participation and, indeed, leadership in some of these consortia.

DR. ALDERSON: And I think that's what -- don't let me get out of bounds here, but I think what the CPath Consortium is a model that can be used focusing on those particular opportunities in the Critical Path document. Gail.

DR. CASSELL: Kind of along the same lines, Norris, I've been wondering, and in particular, because each of the centers do differ in terms of their management of research, as you've pointed out a number of times to us. What is the role of external expertise in helping to establish the priorities or monitoring progress towards priorities? How has that been handled in the past? Do each of the centers have an external advisory board that meets with some degree of regularity to help with that, or how is outside opinion sought?

DR. ALDERSON: Some of the centers have external peer reviews on a regular basis, not all of them. That's one avenue that I think the centers that have that scheduled peer review, they rely on that

tremendously to help them guide in terms of priorities. I think I would respond by telling you that that is probably the case in probably two centers. The others, it's an internal process of center management, particularly reviewers, review management and research management reaching some agreement based on their projection of priorities that are coming, deciding what the priorities should be for the research programs. If the center directors disagree with me, please speak up.

DR. WOODCOCK: With FDA it's also a little bit more complex, because we do have - I don't know how many - a whole lot of external advisory committees. And it isn't just the progress of their search itself, although, the technical quality of the research is extremely important, but it is then subsequent integration of the research into the regulatory standards and the review processes of the various centers that is extraordinarily important, so this has to be a more seamless process starting at the research going all the way through to implementation of standards and feeding back into what needs there

are for improvement of standards and review processes.

DR. LAURENCIN: When I joined the Science Board, Bob Nurham was actually rotating off, and I guess one of his major accomplishments when he rotated off was that actually he had just completed a review of science for CDRH, had a very large report. Now there are 14 recommendations - I just actually saw a copy of it - but there are 14 recommendations that came out of that report. How many of those recommendations that came out of the report were implemented, and how was that -- where was the feedback back to the Science Board in terms of the implementation of those points?

DR. ALDERSON: I'll let Subhas respond to that.

DR. MALGHAN: Yes. I'm Subhas Malghan sitting in for Dan Schultz, who is out of town. The 2001 review that was done for CDRH was clearly what I call paved the ground for subsequent reviews of research within the center itself. The 14 recommendations, I cannot give you, save that we implemented 13 of them. I think most of the

recommendations have been taken very seriously and changes have been made.

One of the major recommendations was to do a science review of the science lab in CDRH. So since 2001, we have been conducting sort of what we call a peer review process at two levels. The objective of that review has been mostly to conduct research that is of regulatory value to the center, and we do bring in experts within the center and outside the center who are really experts in those areas, and take the recommendations and the entire process is very well documented and this implementation is going on.

DR. SHINE: Dr. Laurencin, I think that -- let me open this part of the discussion now while Norris is still at the podium, but I would argue that as part of our review, we would want to take a look at reports. There have been a whole variety of in-depth reviews of centers, and we're not going to be able to repeat those kinds of reviews, but we can ask questions about how and in what way did those reviews change the direction of the center and so forth. So I think part of the answer to your question is that

should be on our agenda as we do our review.

A major challenge to this board, as you've just heard from Janet Woodcock about the extraordinary range of issues that the agency has to confront, you've just heard from Norris about the complexity of the organization, so the question is how do you meet this charge? If you read the charge, it's an extraordinarily big charge. And I'm asking now for Norris' advice.

One of the thoughts that I've had is that we would initially constitute a small working group which would, if you will, develop an agenda for review focusing initially on one of the centers, recognizing and respecting the concern that you have about silos, with the notion that by looking at developing both the specific questions and the kinds of information we need in order to give a report about this, that by focusing on a single center initially we would be able to articulate some of the criteria that we would use, and then plan to extend those over the agency. And in the course of doing that, look at several crosscutting themes. But I think a real charge to us is going to

be how do we get enough focus so that we can add value to an extraordinarily complex area? And I noticed on your list of centers that CDER was the top one. CDER, it seems to me, would be a good place for us to, perhaps, begin this process with a notion that we would spend two or three months working out what it is we need, what we need to know, how we want to find out about it and so forth, and then plan to, over the subsequent period of time, and we can talk about what that time should be, apply that more broadly, keeping in mind that every center is different, that you can't generalize everything from everywhere, but that we need to get some purchase on it. So I wanted to get your feedback before the committee begins its deliberations as to whether you thought that was a sensible scheme in terms of how we might get a handle on the situation.

DR. ALDERSON: I think in the context of developing the process you want to go through, I think you almost have to do that from a context that you're going to feel your way, probably, initially. From a process developer perspective, either that or some

other shortened way to look at the entire agency is going to be needed. I think a concern we're going to have is the time frame that you get into when you do this, and then you have to come back and redo it from an agency perspective. And Dr. Von Eschenbach has a point.

DR. VON ESCHENBACH: Mr. Chairman, I might suggest a couple of things to just frame how we might go forward on this. First of all, I would look at this as a continuously iterative process in which recognizing how incredibly busy members of the board are, and the fact that you have day jobs, and also the fact that members of the FDA are constantly engaged in moving the freight every day, we need to sort of smooth this out, I think, over a period of time, and move continuously from meeting to meeting with an ongoing agenda so it'll be iterative and it will go on continuously. And, therefore, there needs to be a continuous liaison between the board and with the FDA. And I think certainly channeling everything through Norris presents and appropriate plug-in from the FDA standpoint. And then you, as the board, can decide

how that should occur from the board's perspective, whether it's you, or however that plays out.

Now as far as then looking at the portfolio, I think you're correct that you have to drill down to at least some grain size so that you really have some substance upon which to draw some impressions, conclusions, and then subsequent recommendations. But I think if we find ourselves in a process then we go segment and segment, and have to go very, very, very deeply into any one particular component, then the time line is going to be such that before we ever get to what I really would like the board to be providing, which is not so much a review of very fine detail within that research portfolio, but really much more the macro questions that Janet framed, which is portfolio balance, where there are gaps that we may not be addressing, and where there are areas where we could find greater efficiency by not having duplication, but more complementarity.

I would think that the board will move down but move across the portfolio much more rapidly, and I would hope not get consumed by a deeper and

deeper and deeper analysis of just one segment; because you could spend a year, perhaps, or at least a long period of time, and then we would miss the opportunity to get the macro questions addressed, which is where I really would like the board to focus.

DR. SHINE: Dr. Roses.

DR. ROSES: I would agree with that. It's a typical organizational question of matrix versus line. And in this case, we've asked 76 questions, which are critical, and we have an organizational way of assessing which ones of those questions are critical to which line in the organization. And, perhaps, one way of attempting to do the review of how the organization is adapting and reacting to its own prioritized important questions would be to see how that was matrixed across the organization, so that for this question there is this kind of activity, there is this kind of synergy, there is this kind of outreach, there is this kind of partnership; as opposed to doing it typically line-by-line.

DR. SHINE: Thank you, Allen. That was a very good observation.

DR. ALDERSON: I think we got -- I would advise you to avoid getting down into the weeds of individual projects that our center is conducting. It will bury you and we won't get where we need to go.

DR. SHINE: I think we agree with that. We agree with that entirely. I think that's one of the reasons why we would want to look, for example, at what's happened with in-depth reviews, not from the point of view how did they impact the priority setting, but not the details of the -- in other words, it's a process-oriented activity as opposed to a detailed scientific. This is not peer review of science.

DR. ALDERSON: No, absolutely not.

DR. SHINE: And I think we all agree with that. Let's go on and hear from Ms. Mullin, and then we'll have an open discussion. But this is, I think, where we want to get by the end of the session; namely, what's the general approach we're going to take to move forward. Thank you. Dr. Mullin. I should have given you your proper title.

DR. MULLIN: Thank you. Let me make sure

I got the technology down here. Dr. Von Eschenbach asked me to talk about how we address - I'm the head of Planning. I try to help our agency with its strategic planning and facilitate that. He's asked me to talk about how we address research in the context of strategic plans, and as he said it, are we doing the right things to pursue our FDA mission, and also to pursue a vision that Dr. Von Eschenbach has articulated. This is a snippet of, I think, the vision of approaching an era of personalized medicine, delivering the right treatment to the right patient at the right time, and that we're at the bridge to development, so I wanted to find a bridge, because I really like that imagery, so I've got one in here. I'm not sure where in the U.S. that bridge is located, but it's kind of a nice image, and I've learned a little bit more about Power Point in the process.

Let me begin by articulating the FDA's unique type of research. And, again, this is my planning perspective, but that the regulatory research that we conduct can increase the quality and the predictability, and efficiency of FDA's processes, and

also the processes of the innovators and the regulated industry, and has a very unique value-added, I think. That research is, I think, fundamentally applied. It yields findings that translate, basically take the science and translate that into more accurate and specific regulatory standards. And I really want to point out this, there are two types of uncertainty that I think that this helps with, and this is echoing, I think, what Dr. Woodcock said; that scientific and technical uncertainty, so what's the evidence of safety and effectiveness? What do we know about what constitutes good evidence, and that's a scientific concern. And that's really important for the development, obviously, of new medical products and food technology, and to assure the safety of manufactured products.

It also can help us reduce regulatory uncertainty. By that I mean, what does the regulator want from us? If you're an innovator and you want to put together an application, that's another level of uncertainty. What do they expect? I mean, what's going to constitute the evidence? Let's get it right

the first time so we can get the application approved on the first cycle, and so what's another obstacle to innovation here is the lack of regulatory certainty, or if we can reduce the uncertainty and make that process of technology development and adoption more predictable, reduce the business risk associated with that, and open up the path to innovation in products which really serve our public health mission. And so this type of research that we engage in helps to produce a more predictable regulator, and a better informed and more transparent and consistent regulatory process, too, and that's really important for our mission.

The President's management agenda has a performance budget integration requirement, and that's actually a useful tool in making sure that our research is linked to our strategic goals as an agency, because all program spending has to be linked to an agency's long-term strategic goals. And so if we think about trying to reach our vision and our mission here, well, what you see here are the four - they're a work in progress, but FDA's identified

strategic goal areas. We have four long-term goal areas that really reflect our business portfolio in a very broad sense for the whole agency. And they're a little wordy, perhaps, but we're sort of developing them across the agency, and I'm going to focus on the two you see bolded with the examples that I have to offer.

The first goal, increase access to innovative products and technologies to improve health. Clearly, our mission of protecting and advancing public health, that access to new technology is critical. The second goal for us, protecting and empowering patients and consumers, post-market safety, and those issues. And improving product quality, safety, and availability is another very critical goal. This is the manufacturing quality, and then transforming our infrastructure and our administrative systems. So I'm going to focus on this first goal.

I'll give you an example of my kind of simple construct, but I think the way I see the research feeding in and helping us. One of the long-term goals we have in this area is to spur increase in

the number and the quality of marketing applications for unmet health needs. We want more medical technologies and healthy technologies for food out there, but we can only provide a way to spur that innovation by lowering the barriers in terms of uncertainty and making that easier because the market has to do that. We don't do that.

How can we lower the barriers? Well, identifying specific regulatory and scientific uncertainties that may serve as obstacles to adoption of new technology, taking new approaches. Well, that translates into the research needs that get identified. What do we know, and what do we not know that's generating uncertainty that prevents development and innovation in a certain area? The identified needs, and here you might think, for example, the Critical Path list of opportunities - here are unmet needs that need to be addressed, help us to focus our applied research. We tend to focus our research funding on those questions that need to be answered, and that research developed provides scientific findings that then enable us to update our

regulatory standards. And examples of the way that will help us update our standards, this will help us to qualify biomarkers for regulatory decision-making, identify surrogate endpoints that would be acceptable as a basis for approval, streamlining clinical studies in many other areas, so that's the fruition of this kind of research.

How would you identify those needs? Well, in the context of drug development, I'm sure everybody is familiar with this picture. I'm not going to spend much time on it, but in the course of interacting with innovators you see where they're getting stuck, and you identify areas where there are uncertainties, people aren't going there. And that's one way to help identify opportunities for trying to reduce those technical and regulatory uncertainties.

Here's the other one I just want to talk about briefly, but I think this is one of the big areas of our scientific application and need; improving product quality, safety, and availability. We have two broad goals here; maximizing medical product quality and food and tissue safety, as well as

their availability so that they're safe, but they're available for use, and preventing harm from substandard processes and products. Across all the centers I believe we have research that addresses these kinds of uncertainties and regulatory obstacles.

For example, in biologics, product characterization so that you can actually identify the new product so that it can be studied. GNP problems that are identified across the board with product contamination, product materials failure, and those kinds of problems help us to focus research in areas across the GNP and product manufacturing areas. And that yields scientific findings, and engineering solutions that, again, enable us to update the regulatory standards. So examples here, quality by design concepts, the new reference assays that are needed to develop to manufacture new biological products with consistency of quality, material standards, just a few examples. And then very critical - technologies to help detect contamination in food, in blood, in tissue products, that detect counterfeit products, and make sure that the products

that are out there are safe for use. This is how we would link this to our strategic goals, our research work.

The centers have a very aggressive approach to managing research within the centers as we've already heard, centers determine the allocation of program resources for research among what's available in their center. They determine what research projects to fund, they publish their plans for research, they systematically evaluate those projects, they publish the findings. And Norris convenes a group of the research leaders across the agency, and there's an information chain there.

And how do we ensure that the research is consistent with priorities? Well, this is probably pretty basic, but aligning program goals with our priorities and then targeting the fund to research that delivers the science to achieve the goals in something like the process I think that I just described in a real simplified way.

I think we design public/private partnerships, and we need to make sure that those

partnerships focus on our regulatory decision-making needs, that maybe other partners in that relationship may have aligned needs, they may have slightly different needs. We have to make sure we get out of that research projects what we need for regulatory decision-making. And regulatory decision-maker, I think as both an advisor to the projects because they help bring in their experience with the problems, but they're also a customer for the research function, because then that work will turn into standards for future regulatory decision-making.

Now when you're talking about a way to take a slice, a goal area might be another way to take a slice. Yes.

DR. ROSES: Up until your management slide, where it then reverted right back to the centers, and I think if you line the 11 centers up and you find the places in common that each of these 76 and have your matrix management of managing the science, and managing the problem, as opposed to it being encapsulated within these would be a much more efficient way of doing it. And certainly, there are

models that you can follow from other organizations and industry that does it that way.

DR. MULLIN: So work across the dimensions that I --

DR. PARKINSON: Yes, if I could pick up on that, because I really like that way of approaching it. I mean, the agency has spent a lot of time getting external input, and I suspect a lot of internal energy and time discussing it and coming up with these 76 topics. And I realize that doesn't deal with the food side, but there's no reason why the process couldn't ultimately -- and when you look at them, these are really important cross-center, cross-discipline topics, which is part of the reason they're so difficult to deal with. It doesn't matter whether you're in an agency like this, or whether you're in another organization. So I was thinking about this as you were talking, because for each of these areas, it's possible to use the same process to identify the internal FDA agency stakeholders - that's a business word I learned - and they use it in the agency, too. Good. So we know there are stakeholders within the

agency, but certainly there are also stakeholders in the external community, the same people who gave input into these topics. So then it seems to me that a common process could be used for these 76, to identify those stakeholders, to then get them together and to work with them to identify the technical and scientific obstacles to achieving whatever it is. That's started already in certain areas in the cancer biomarkers area - there were some initiatives in the last few weeks with the agency. Janet, in particular, being very actively participating with a lot of external stakeholders in that area. We even had economists at that particular one. But what I'm talking about here is a common process.

So you have the stakeholders, you do the technical analysis, you look at where the obstacles are, and where the rate limiting steps might be for each of these 76. And then you also try to identify who the natural owner is for these various pieces. Sometimes it's going to be internal to the agency, I would guess. Sometimes it's going to be maybe external, maybe it may be shared, I don't know. And

then you do an assignment of resources available, versus resources not available. We call it a gap analysis, and you identify a way of going forward.

And all I'm trying to suggest is a common process for identifying multi-disciplinary topics that's already been through a public process that everybody agrees are important. And it might be a focus for the committee to begin to interface with the agency, as well; because, otherwise, it's actually quite difficult to look at the enormous expanse of 25 percent of the American economy and identify areas for improvement. I don't know - my thoughts as I was listening to you.

DR. SHINE: Well, this would be a good opportunity now to open the discussion to the board with regard to the charge. Thank you very much, Dr. Mullin. We may still call on you for comments on this, but to discuss a little bit about how we might approach the charge which is written here.

David, I'm very attracted to your approach with regard to the issue of those 73 items. I'm less clear, and maybe you could help me with it, as to how

that will help us understand throughout the agency how and in what way they're doing their business, if you will, from the point of view of the science that they require in an ongoing way. And so while I -- it seems to me that the approach that you're describing makes perfectly good sense in terms of how you pursue the Critical Pathway, having done that, will it fully answer the question of whether we're applying particular resources in the course of the various roles we have in a meaningful way?

DR. PARKINSON: That probably could best be defined by the centers individually - I mean there are individual needs, and then there are multi-disciplinary cross -- these are functional topics. Right?

DR. SHINE: Yes.

DR. PARKINSON: You probably have internal structural, mechanical, analytical needs that are very center-specific, I suspect. And we may need to have dual processes.

DR. SHINE: Please, Dr. Woodcock.

DR. WOODCOCK: I think we, meaning the FDA,

would be pleased to interact with the board around the opportunities list, but it is a separate topic, because as you said, it's sort of getting down to the project level. And I think what Dr. Von Eschenbach has asked you to do is take a broader perspective. But if members of the board are very interested in implementation and how we're going to actually sort of operationalize the opportunities list, we could certainly have a separate discussion with you on that, or as part of this review. But I wouldn't construct the review around that list, because it constitutes examples. It is not intended to be a comprehensive needs list.

DR. SHINE: I had the privilege of serving on a committee co-chaired by Gail Cassell on the overarching aspects of the intramural research program at the NIH. Dr. Cassell, you've thought a lot about these kinds of reviews. What are your thoughts about how we might approach it?

DR. CASSELL: Well, Ken, I do definitely agree with you. I view these as two really completely separate things, but things that have to move in

parallel. You don't want to stop the momentum with the Critical Paths Initiative, and you want that to move forward. I like your idea about the approach to that.

I think as far as the review is concerned, what Paul Marks and I realized right off the bat was going to be impossible to review in-depth each of the institutes at NIH and make the recommendations that we had been asked to make, or answer the questions that we had been asked to answer for Congress. And what we ended up doing was to try to select the two institutes that were at the opposite end of the spectrum, or at least what we thought were at the opposite end of the spectrum in terms of management and also issues, and then did an in-depth analysis of those, issued our overall report, and then after the overall report was issued, then year-by-year there was actually a review of the individual institutes in-depth, and I think that worked fairly well, at least what I'm told from those that received the report it seemed to work fairly well.

So I would suggest, as you have outlined, Ken, that we move forward by doing an in-depth

analysis initially of CDER, not delving into the minutia, but rather trying to develop a roadmap by which we can look at the other centers.

DR. SHINE: Thank you. Other ideas or suggestions? I think, Dr. Roses, the proposal I made was not meant to be an in-depth review of eight silos. It was trying to figure out, and maybe there is a way that we could create a methodology which would provide the matrix overview, and perhaps test that in a couple of ways both across the agency and in individual components.

One of the concerns that I had, and again, I'm just throwing this out for the group, is what kind of information do you need in order to make reasonable judgments about what's going on? What do you evaluate? Who do you talk to? How do you do it in a cost-effective, time-efficient way? My sense was (A) this is not a peer review of the science. It's about the content and the direction, and the priority-setting process.

Secondly, that in order to do it in a timely way, we would have to organize ourselves so

that we are moving the agenda in-between our semi-annual meetings. This is not a meeting-to-meeting project, it seems to me. Thirdly, that we would clearly want to end up with a methodology which was further -- across the entire agency, that this was not designed to be -- how shall I say it -- prescriptive in terms of individual components. And fourth, that we ought to, if we can, minimize the amount of paper and other kinds of administrative shtick that goes on in terms of trying to do this. Dr. McNeil.

DR. McNEIL: Ken, I'm not sure if this is part of where we should be talking right now, but I was impressed with the last talk, which I really enjoyed a lot. And the particular side that talked about increased access to innovative technology to improve health, and reducing the uncertainty about inventors, or companies, whatever coming with products that they hope to get approval for. And I'm wondering, is it possible to look across the various centers and get some sense of what centers are doing better in that area that would then give us a lesson for the future; that is to say, are some centers

specifically having more sets of interactions with their potential clients than others, or is the quality of the interactions different? All this in a way that reduces the number of re-submissions, or the uncertainty, and the extent to which the original applications are formulated to actually get an approval for a drug or a biologic.

DR. SHINE: So this is a combination of perhaps either best practices or comparative anthropology, or whatever in terms of how you do a variety of things.

DR. MULLIN: I think so, just because it was highlighted as one of the key problems during the last talk.

DR. SHINE: Dr. Laurencin.

DR. LAURENCIN: Listening to Allen Roses, I loved his approach, and then listening to Gail Cassell's approach, I loved her approach. Is there a way to combine this? I thought the approach in which -- because one of the big issues is what's happening across the organization, and so is there a way to look -- I thought the approach where you look at two

centers that are at different ends of the spectrum, and to perform an analysis of those two centers, seeing why they're at different ends, what the rationale is, and where the commonality is of purpose, is a great approach, and serves to do two things. One is to understand really what's going on in the centers, but also understand how to move forward in terms of commonality. I thought that's a great idea and a great approach. We've already got the blueprint because you've done it before with the intramural program at NIH, and so I thought that's a great approach to look at.

DR. SHINE: Dr. Swanson.

DR. SWANSON: Yes, I would like to just kind of toss in my vote for making sure that we're looking at more than one, because of the breadth of the organization, the issues that occur, and the opportunities to leverage resources or approaches that exist in the different centers on a shorter time frame than trying to go after silos. Organizationally, you need to look across what is going on in the different organizations so that you can more quickly adopt best

practices and get rid of the things that, perhaps, aren't as productive, so I kind of like a combination of what Dr. Cassell and Dr. Roses proposed.

The most important thing, I think, is to spend some time on what is the process that we're going to use, and then go forward with that process.

DR. SHINE: Dr. Harlander.

DR. HARLANDER: I'm wondering in listening to what Barbara had just said, if there aren't from a process approach some key questions that could be asked initially across all of the centers. Even if you're just focusing on a couple, I'm sure there are some key questions around, for example, how do you get stakeholder input into your priority-setting process. And listening to Norris, there's obviously going to be differences across all of those centers, so just understanding what's happening today from a global perspective, a macro perspective, that would allow you to compare across centers, even if you're only evaluating a couple right now in-depth, I think would provide kind of that macro perspective that Katie suggests you could look across, find best practices

and make some real recommendations.

DR. SHINE: Yes. I should be very clear that whether we look at one or two, or whatever in the initial stages, that was only with the notion of creating, in fact, the template that you would use across the agency. I mean, I think all of us recognize we have to look across the agency. The question is, are we comfortable developing a series of questions that we ask everybody up front, and will that be adequate without looking in more depth some place. But I think it's nobody's intention to just look at a couple of centers. I think everybody agrees we have to look more broadly.

I want to ask the Commissioner to make some comments, but Barbara, why don't you make one last.

DR. MULLIN: Just one last comment with regard to your kind of dichotomy, do we do one first, identify questions, and then follow? And I think that really depends upon the time course in which the agency wants advice, because it's obviously going to take several months to do an in-depth analysis, and

then several months after that to develop questions. In a different venue, we could be developing the questions and answer some of them by going across all of the centers at the same time, so I really think it depends upon who wants what, when.

DR. SHINE: Let's ask the Commissioner. We have a number of center directors here. We want to give center directors an opportunity to get their two cents in before we come to any conclusions here.

DR. VON ESCHENBACH: I think this has really been, for me, a very rich discussion, and I really have enjoyed it. But one of the things that I came to appreciate, and why I asked the Chairman to give me an opportunity to kind of sum up is, clearly, it's very important for me, for us to express the expectations that we have for this outcome as clearly and as precisely as we can, because otherwise, if you go on to do things that are appropriate and very well-meaning, but they're not actually addressing those expectations, then at the end of it, we're both going to have a very frustrating experience, so I thought what I'd do is just backtrack a little bit, because I

think the slide that Theresa Mullin put up helps me kind of reiterate again what I think some of the expectations are with regard to this process and this outcome that we're going to go through. And I think I like a lot of the parts and pieces that were put on the table. And what we're looking forward to is a process, and it's a process that really gets us to being able to use research within the agency that accomplishes and meets the mission and the content of the mission that we're defining for ourselves. And as Janet has often pointed out, the FDA of the future to meet its challenges and its obligations across the entire portfolio, needs these new tools. And the critical path is just one way of trying to define what some of those tools might be, and - we have 76 different kinds of tools that are now going to have to be in this toolbox, but that's not really what I think, the expectation and the focus that I have is that maybe a little further up from that in -- granularity is helpful to look at this in a way that says we are going to be defining the content of this research that's going to go on within the FDA, it's

going to give us what we need to be able to use science to accomplish that mission.

DR. SHINE: Commissioner, as a cardiologist, I want to reduce stress on the audio guy. He's getting very nervous because you've got to stay close to the --

DR. VON ESCHENBACH: Okay. I'll stay where I am.

DR. JOHANNESSEN: There is a pointer on the podium.

DR. VON ESCHENBACH: It's the Italian in me. I've got to walk and use my hands. And maybe just backing away to a different model, an investment model might be helpful. What my expectation is, and what I hope the board will be able to come to is to help us with portfolio management, not necessarily at this point, drill down into the various parts and pieces of the portfolio to do a stock analysis or to investigate a particular investment in terms of its yield, but really be looking at the balance within that portfolio, and is that portfolio helping meet the needs that we have as an agency. And the point of

that is by looking at the portfolio broadly, what has become increasingly apparent to me is the context that the Chairman alluded to, is that this portfolio is now inter-dependent. The parts and pieces do not exist in isolation. They now have the need to be integrated in the sense that the research is inter-dependent. And we have to find those gaps where we have gaps, and we've got to find those places where there's duplication or overlap that we could then streamline and make more efficient, and position the portfolio in a way that it is really meeting our entire goal. So as you look at this, I think it's going to be a much more macro perspective. You'll have to delve down into the portfolio to some degree to be able to understand the content and substance.

And if a way of beginning the process, to have a focus that out of which, Dave, I agree with you, may come just simply then a lesson learned as to how to do this, and we get a template as to how to go through this, we would be able to go through it in an iterative way over a series of questions. We may start out with the issue of, for example, increasing

access to innovative technology and improve health, and we have our qualified biomarkers, streamlined clinical trial, some of the topic areas that are in that Critical Path; not the 76 pieces, but at least the topic areas. Could be an area of first cut to get to the point that Allen's talking to, how you look at this as a matrix. How do we look across what we would define as a programmatic area or a horizontal integrated arena that we can look at this portfolio and say is the research portfolio addressing this, and where is there gaps, where is it addressing it in multiple places that are creating simply unnecessary redundancies that by greater integration and more seamless integration you could, in fact, eliminate that and enhance your ability to use those resources in some other more effective way. And we will need that information to operationalize this portfolio.

It will remain my responsibility, our responsibility, to make the ultimate decisions as to what this portfolio is going to look like, what research is actually going to go on in all these various parts, which sectors we're going to be

invested in and what particular stocks are going to occur, and that's all operationalized by the center directors. But you're giving us the broad perspective, and the wisdom of what an ideal portfolio would look like given the macro world that's out there, and given what we have in the way of resources and opportunities.

So picking something that identifies a crosscutting initiative, it will only be one of many that you could pick, but pick one, go across the portfolio in enough detail to ask the question, is the portfolio, is what's being done ideally integrated and organized in a way that's meeting that end, are there gaps, are there overlaps, are there duplications, and how could you position that horizontally in a more effective way to get that outcome? And then we'll do it again with a different issue, and again with a different issue. And in the process of doing that, you're going to be getting insights into the content and quality and caliber of those individual investments and will comment on those in terms of what you think in terms of individual quality. But it is a

different kind of review. My expectation is for a different kind of review.

I hope that explanation of my expectation serves a little bit to further frame how you think you might be able to most effectively carry that out.

DR. SHINE: Comments or responses? Yes, please, Dr. King.

DR. KING: I don't know if this would be helpful or even relevant, but I spent the last year at CDC in an office called Strategy and Innovation, and part of that was the idea of how do you drive strategy in a public agency or public organization, or should you, so that was one part of it. The other part at CDC we were struggling with was the same thing you're kind of talking about here, and they've decided, whether it was right or wrong, it's still controversial, is to kind of turn 250 diseases and body parts, as you've said, into new strategic health impact goals, and those goals really structured and focused on enhancing public health across the life time and improvement, which is the exact mission that you have. So the question would be what's - the role

of current science being used appropriate here, and how should it be leveraged? And what CDC decided was, whether it's relevant or not I'm not sure, but they went through a process which was interesting, a future initiative which they had a group of strategic imperatives, and then they went and looked at how do you enhance health across the entire lifetime? And they used overarching goals across the entire agency, and re-established those goals and how they related to enhancing the public's health across the lifetime.

For example, enhancing adolescent health. When they actually looked at it, there were 17 different divisions within CDC that had resources and programs in adolescent health. I think there was no time that that group had ever gotten together before, but when they looked at strategizing and how you might integrate, is there a better way of improving adolescent health? And the answer was, we should have looked at this before. It's a different set of lenses by looking at an outcome, the outcome is the improvement and enhancement of public health. Once you decide on that, then the map goes backwards rather

than drilling down into individual programs and trying to move ahead. I think it was - like I said, it's still being worked on, but it was kind of a light that came on for a lot of people.

DR. SHINE: Okay. Any of the center directors want to make observations that would be helpful to this process? Please, Dr. Slikker.

DR. SLIKKER: Bill Slikker, National Center for Toxicological Research. I really like the idea of doing some survey work up front to help sort of guide the process, because not only can you get a more integrated view of what's going on across FDA, but also you can learn about what other kind of review processes are already in force and be helpful to you. For example, at NCTR we have the mandatory peer review of the individual scientists in a cyclic manner, but we also have a scientific advisory board that does in-depth review of each program or division at an on-site visit-type opportunities, so that's information to be used by this more global group to really help move the process forward. And I'm sure other centers have those same kinds of opportunities

that you'd like to know about.

DR. SHINE: Thank you. Other observations? Steve. Dr. Galson.

DR. GALSON: Thanks. Of course, I agree completely with Dr. Von Eschenbach's expectations for you all. I want to focus on one specific aspect of it, which is that you all have your specific research interests or interests in specific parts of our program. I think the challenge here is trying to figure out what the agency actually needs, how will we use the product that you could produce for us to make our very, very difficult management decisions. And as a witness and participant in many of these sort of prioritization and peer review processes through many years at different agencies, I would say the majority of these sort of reviews and reports go sitting on somebody's bookshelf and are not that useful, so I think the real challenge for you is to sort of put aside perhaps your individual interests and look at really what does the agency need to help us make decisions in the future in a very, very limited resource environment where, of course, the imperative

for us to work more closely together is there. There are also specific product needs at individual centers that are going to drive some of the research priorities, but really looking at how we can focus and spend the limited time that you have to make a product that we'll actually use is a very important thing for you to focus on.

DR. SHINE: I may be naive, Dr. Galson, but I see us looking at potential gaps, for example. But from the perspective of how does the entire agency function rather than how did I get my science done, and I think that that's not what we're about in terms of the special interests of people on the committee. Other comments? Dr. Woodcock. I'm sorry. Go ahead.

DR. BUCHANAN: Thank you. And before I give my comment, I just wanted to say that Dr. Brockett asked me to express his regret for not being able to be here in person.

I guess as a client of the science board in the past, and being highly satisfied with the types of external reviews, we hope in the long term that we don't necessarily do away with all of the sort of old

fashioned reviews, that we can continue to schedule them in the future because we found them very important for our strategic planning. But in terms of the types of portfolio reviews here, these are, at least in my mind, a very different beast than what we've done traditionally. And traditionally, we've spent a lot of time asking scientists what they're doing and how they're doing it, and I see this more as a review of, if we're taking a business model, of the clients. And we think that this kind of review would need to focus more on the users of the knowledge and the technologies that are generated within the FDA, and also would have to include some of our stakeholders in this process. And I think that this is going to be a real challenge for you coming up with the correct metrics to how to measure the success of the program currently, and how to measure the success of the program as you've provided some advice in terms of where it should go. So I think it's going to be a real challenge, and it's certainly going to deserve some thought about are we asking the right questions of the right people?

DR. SHINE: Thank you. Dr. Goodman.

DR. GOODMAN: Well, there is so much here, and I think that's part of what everybody's grappling with. And I, just from my perspective, I think what would be really helpful to us, I don't think you can do an entire review of the program down to the depth of projects as has been said, and I don't think you can invoke all of our stakeholders because they are so diverse and so rich, and that's a process that even we in the programs try to do but don't always have the time and resources to do.

I think what would be helpful to me, at least, and probably to the agency, is to look at what we're doing, perhaps identify best practices, also best practices, and this is not so much comparing one center to another, but what are the opportunities that some have identified and are available that seem really good?

Many of you have outside experience with other scientific and government organizations and academia, as have I, and I always say to my people what can we learn not just from the FDA, but from the

rest of the world in how we do, so you bring your experience to that. I think that's important.

I also think we should keep an optimistic view of this. We have a very resource constrained environment, but we also should ask ourselves well, what is it that we can uniquely do and should be doing to meet unmet public health needs, and to help get these medicines of the 21st century, and how do we use our resources to do that?

Some of the things that come up with me are not only what are good processes for getting input? For example, I've directed people to bring our entire programs in different program areas to our advisory committees and get input about those programs, so that's one model that I think has been helpful. But then what characteristics should we base our priorities on? What is it? Is this the unmet public health need? Is this stuff that nobody else is going to do? And there's a lot of factors we have to consider when the resources are limited.

Most parts of the agency have identified partnerships and opportunities for leveraging; but,

again, are we fully taking advantage of those? Can you help us understand good ways to build those, to build support for those, et cetera? And I think those are kind of the main things. And I think we can't shy away from the resource issue either, and again, that's part of the leveraging, but it's also part of our reality. So I think this sort of best -- and I want to -- because the Critical Path was brought up, and I thought Janet answered it really well, and I want to just make clear that the centers support that initiative, but that is a very different process. That was saying if we working with outside stakeholders could bring various resources and look at some unanswered opportunities out there, what are some of those opportunities? It wasn't a systematic attempt to identify every single opportunity. Different stakeholders were engaged to different degrees, depending on a variety of factors, and I think that tells us a lot of important stuff. And, again, our view in our center has been that our center should be very involved in that, and look at those lists, and see where those opportunities are, and what

things we can help with on our internal area, so I think it's very important to make this connection, but to recognize there are things like you're making X vaccine, and we all know that this assay is not very good. Where it may not ever make it into there except in a generic manner, yet it could be very important and very low hanging fruit for public health benefit, so that's where I think you should understand how we, as an agency, see differences between these programs.

DR. SHINE: Dr. Woodcock, I think you wanted to make a comment.

DR. WOODCOCK: Well, yes, I had a couple of things to say. First of all, I strongly agree with Bob that we have to think about the regulatory needs and the mission, and I really believe that's where you need to start. If you're talking about portfolio management, it isn't like what fun science we want to do. It's really how do we answer the critical needs that we need to answer, critical scientific questions to get our mission done. And, therefore, I might encourage you to actually go around and as part of your original screen or whatever, to ask the centers

what they think the fundamental questions are, the fundamental scientific challenges they are facing right now, and get a short list from each group. And maybe you could see how much that overlaps, just sort of one thought.

The other thing I wanted to say is, we have a business model which Theresa has presented part of. We can provide that all to you and it organizes all our business processes and activities into just a few areas, and it turns out there aren't that many actually, so there's great commonality across the centers, not in content but in process, and what the activities that they actually are engaged in are. And that may be helpful to you.

We're engaged in fleshing out this model to have specific action items and measurable deliverables and so forth against these goals that we've developed, so that might help also when you embark upon this in kind of organizing your thinking, because what was said about what CDC did, we've already more or less thought through that at the FDA level.

DR. VON ESCHENBACH: Yes. I've been reluctant to put a very, very specific thing on the table because I wanted to allow this to be as broad and as far-ranging and enable the discussion. But, for example, this particular slide talks about qualified biomarkers, which is clearly a part of the Critical Path. But then you take that from the point of view of what we need with regard to being able to have markers for efficacy and markers for safety, and then you can drill down from that to the role of pharmacogenomics or toxicogenomics. And we have activity going across the entire FDA in those specific areas, and it would be useful to look at pharmacogenomics, for example, across the entire dimension of the FDA and ask the question where are those opportunities for the synergy, where are the gaps, what's going on in other areas that need to be simply complimentary to and integrated with? And it's that kind of analysis that I think is very helpful for us then in terms of defining what our investments should be, and that area that defines the uniqueness of the FDA, defines the value that we can provide to

driving to those endpoints, and becomes a major contribution in the regulatory process, and there may be ten other areas, and you may choose something else that's an exciting first focus.

DR. SHINE: Commissioner, let me suggest an approach to this process so that we could take next steps. We have a number of people on the board who have some experience with a variety of these kinds of reviews. I think we've had a pretty good exchange of some of the various themes that might go into the reviews. I also think that the Henry Kissinger of the science board, Cato Laurencin, has quite wisely said that we're probably going to want a combination of a couple of these approaches in terms of how, in fact, we do it.

What I would like to do is to identify a small subcommittee of the board, ask them to work to develop a template for how and in what way we're going to want to proceed, and that template could take the form of primarily a survey, or it could take the form of a series of issues to be explored with or without a survey, but the two would be presumably connected.

Because, as I say, I think we need to move with some deliberate speed. We would try to develop that template and have some kind of an iterative response whether to you or Norris, whoever you think is appropriate. And before the fall meeting, we might want to test that template in one or two places. This is where I like Gail's notion of taking a couple of places in the organization with the idea that at the fall meeting we would try to agree on a formal process by which we're now going to look across the entire agency. At that time, have a plan that's been articulated with enough detail so that people would really understand what we were talking about, and we were getting much more concrete.

I think, Jan, it's legal for us to have such a subcommittee. Right?

DR. JOHANNESSEN: Yes, I think so, if we take it from the perspective of your information gathering and planning, as opposed to --

DR. SHINE: With the idea that they would be coming back to the fall meeting with that information.

DR. JOHANNESSEN: Yes. And that information would be discussed at our public meeting.

DR. SHINE: Does that make sense to the board? Gail?

DR. CASSELL: It seems to me too slow. Well, I may be wrong, but I would think that it will decrease the utility of doing it if we string it out over a two-year period, and just to develop the template - were you actually saying develop the template and try it out?

DR. SHINE: Yes.

DR. CASSELL: Okay. Between now and --

DR. SHINE: Yes.

DR. CASSELL: Okay. I'm sorry.

DR. SHINE: I'm suggesting --

DR. CASSELL: That's fast. All right.

DR. SHINE: If the Commissioner agrees, we would develop it hopefully over the next couple of months. Then we would test it in a couple of places. That would begin the information gathering, but it also would tell us something about the reality of what we are doing, so that by the time we were at our fall

meeting, we would have some experience, and be able to say this works, this doesn't work. We want to do a formal survey for the whole organization, and this is what it would involve and so forth. No, I'm suggesting some action items, and that's all information gathering so Jan sleeps well at night.

DR. PI-SUNYER: I wonder when this is being done by the subcommittee, I think one of the really important items that to me is very unclear, is this whole leverage and the outside to inside collaboration, and how this works, how the individual scientists do it. Is there any kind of direction in that way? Is there any kind of encouragement? And how much money is it, we didn't hear today at all. How much is involved here in relation to the $140 million internal? And it seems to me incredibly important in how you base criticism or correction, or recommendations, what this relationship and leverage is, and how important it is to the whole --

DR. SHINE: And I would believe that's one of the kinds of information that we need to gather in that full range, because that's part of the science

activity.

DR. VON ESCHENBACH: I need a little bit more clarity about that. I'm not sure I understand why budget, and why investments are relevant to an assessment of the science, and assessment of the impact of the science, because I think those budgetary issues are internal operational issues, and not necessarily strategic planning.

DR. PI-SUNYER: But they determine to a great extent what kind of research is being done, as I understand it.

DR. VON ESCHENBACH: I would prefer we didn't do that, that I would not want the financial constraints to be defining the research portfolio, but rather, the research portfolio be defined by the strategic opportunities and priorities. And then it follows on after that to find the mechanisms for providing the resources to carry that out.

DR. SHINE: I didn't interpret the question quite that way. I interpreted the question to mean if you look at the science activity of the agency, what is the nature, the quantity, the focus of

the research which is funded extramurally, and what impact does that have on the overall research portfolio internally? I mean, clearly if, for the sake of argument, a particular center is devoting a significant amount of resource to solving the problem of substrates, for example, but there is a collaborative agreement with the NIH, and there's a significant amount of funding available, that may be a perfectly appropriate way to handle that particular problem. No?

DR. VON ESCHENBACH: Disagree.

DR. SHINE: You would prefer not to look at extramural sources.

DR. VON ESCHENBACH: I would prefer the analysis as it's evolving and being implemented, be looking at the portfolio from the point of view of not the financial investment associated with it, but looking at it --

DR. SHINE: But the content.

DR. VON ESCHENBACH: The content, exactly. But we can define the content in terms of the magnitude of that content and the scale and scope of

that, I think, based on the scientific -- based on the research activities being conducted.

DR. SHINE: But, for example, if you have a collaborative agreement with an outside -- and the content of that is addressing the regulatory needs, that becomes relevant.

DR. VON ESCHENBACH: Oh, that counts. Absolutely.

DR. SHINE: Okay. I think that's where we're going.

DR. VON ESCHENBACH: No, no problem with that.

DR. SHINE: Yes, I think that's what I understood.

DR. VON ESCHENBACH: Yes, I'm fine with that.

DR. SHINE: It wasn't the money, primarily. Any other comments or suggestions from the group? And I'm going to talk with several of you about being the subcommittee, because we'll have a fair amount of work to do over the next couple of months to get this moving. Thank you all very much.

Thank you, Commissioner.

DR. VON ESCHENBACH: Thank you. Thank you very much.

DR. SHINE: And we'll try to move the agenda. We'll take a 15-minute break, and then we're going to come back to make the world safe for drugs.

(Whereupon, the proceedings went off the record at 10:35:58 a.m. and went back on the record at 10:52:12 a.m.)

DR. SHINE: Drug safety continues to be an area of interest and importance, and we are pleased to get a follow-up with regard to the FDA's activities in this area. Doug Throckmorton is going to give us an update with some additional presentation from Paul Seligman, and we look forward to this briefing. Thank you very much.

DR. THROCKMORTON: Thank you, Dr. Shine, members of the board. We'll wait until Jan gets my slides up here.

DR. SHINE: He's multi-tasking.

DR. THROCKMORTON: Yes, I see that. Thank you very much again, Mr. Chairman, for asking CDER to

come back to you and continue the discussion we've had about drug safety. There are sort of three things that we'd like to talk with you about today. All of them related to things that we've talked about at past meetings. This is, I think, the third meeting where we had conversations about drug safety.

After my talk, you'll be hearing from Paul Seligman, to give you some information about the kinds of databases and informatics, things that we in CDER are using to address drug safety. And then that follows some comments and some questions that some of you had had at previous sessions.

I'm going to have a talk with two parts to it, and the last part of that talk will be to discuss the ongoing activities that the drug safety board has been undertaking, with particular focus on the priorities. And if you remember at our last meeting, we had a conversation about the priorities. The board has now spent a fair amount of time discussing that, and I'm going to discuss some of the things that they have really chosen to focus many of their attentions on.

I'm going to begin my talk, however, with a brief discussion of where the drug safety board fits in the larger context of drug safety in CDER. And in particular, to contrast its role versus some of the more public venues that the center has been using to talk about drug safety, get public input in particular advisory committees. So after a brief update, a brief review of what the drug safety board is for the new members of the board, I'll be talking about the role of the drug safety board, and then some of the drug safety board activities that we've had since the last time that we met.

So to briefly summarize, just to recall that the drug safety oversight board was formed in 2005 as a part of the CDER response to our new needs to communicate and manage product safety. Its task, the task that Secretary Leavitt gave to us, was to provide independent oversight and advice to the CDER center director, to Dr. Galson, to aid in the management of important drug safety issues and policies, and to make certain that we are maximally efficient as far as communication of those emerging

safety concerns to healthcare practitioners, to patients, especially through the website.

The drug safety board membership, again, just as a brief recap, includes the Deputy Center Director for the Center for Drugs, the board staff is headed by the Executive Director, Dr. Susan Cummins, and the board is constructed by not only members from within the Center for Drug Evaluation Research, but also importantly includes people from the Center for Biologic, CDRH, and from members of the NIH and the VA, which obviously give us a new opportunity to get people's voices from outside of the FDA, give us a new voice on the way we're approaching drug safety.

So where does this board, where does this drug safety board fit in the larger context of how we've been approaching drug safety? And especially, what I'd like to call the complimentary role that I view the drug safety board and the advisory committee meetings as having a mutually beneficial role.

I strongly believe the drug safety boards do not replace the advisory committee meetings, and they do not reduce the need or the availability for us

to obtain necessary public input. This slide sort of in two columns contrasts those two kinds of meetings that are held in the Center for Drugs, the drug safety board meetings, and the advisory committee meetings. Illustrates, one, many of the overlaps, because I think there are overlaps in terms of the kinds of information that the two boards are able to see, and the important differences, particularly in terms of the venues, and in terms of the mandates that the two boards, two types of meetings have.

Obviously, both groups are able to review information on product-specific issues. The drug safety board tends to see many issues at a given meeting. They're asked to look at a variety of things in contrast, an advisory committee which is typically focused on a single drug or class of drugs so that you can really burrow into the details.

CDER's drug safety board is a process-oriented, has a process-oriented function in contrast with the advisory committees, where we're typically asking for input of a more regulatory nature, we're asking questions about whether a product is

appropriate, whether the risk and benefit of a product is appropriate to consider it for marketing, asking about assessment and management of new safety risks.

The drug safety board is a venue where CDER is able to resolve internal organizational safety disputes. In contrast, the advisory committees are set up, are mandated by Congress and have a clear goal of being a venue for obtaining public input, where needed, to assess our decision-making. Obviously, discussing safety and efficacy of novel products prior to marketing, discussing emerging safety concerns for marketed products, and discussing risk management programs, either pre or post marketing, for those identified safety risks are all things that advisory committees do, in contrast to the drug safety board, where we tend, again, to focus on process internally, more on a mechanism to make certain that CDER is approach these drug safety issues in the most effective manner.

The advisory committees, as I said, have access to much of the same detailed information that the drug safety board is looking at, including product

developer's data and analyses, CDER efficacy and safety evaluations, CDER reviews from other disciplines including preclinical toxicology, clinical pharmacology, and statistical reviews. Obviously, the material related to post-marketing adverse events where we often get reports of new safety signals, and summary information about drug use. So the advisory committees see the information, and there's a mechanism for us to make public this same available information.

Advisory committees also frequently discuss safety. The impact of the drug safety board has not been to reduce the discussion about safety in a public venue. Having been a division director in the Division of Cardio Renal Drug Products, I know that as a component of almost every one of my advisory committees, drug safety was considered. Whether it was considered in a larger context of efficacy and safety, or whether there was a focused meeting only to talk about safety, it always was a part of that public discussion. Obviously, more recently we have had relatively high profile meetings

directed more or less solely at identified safety concerns, and I've highlighted two recent examples, the considerations for remarketing of Tysabri, and the two advisory committees that were held to discuss the cardiovascular neuropsychiatric adverse events reported for drugs being used to treat ADHD.

FDA, in addition, finally has other mechanisms to reach out to obtain public input; so, again, the notion is the drug safety board is not reducing our need or our venues that we're able to use to obtain public input around drug safety. An example is the Part 15 hearing that we held in December, where we asked public consumers, academicians to tell us what they thought of the job we were trying to do as far as communicating drug safety. And I know that Paul Seligman was there, and several of the others of us here, and we got an earful over a two-day period of time. It's clear that the public supports our goals, the goals of the new FDA communications, the new efforts to communicate about emerging drug safety risks. However, there was clear reservation that many of the communications that we were putting forward,

some of these new kinds of communications were confusing. People weren't clear of exactly the goals, weren't clear exactly the audience that they were targeted at. And also, that the website, in particular, was difficult to navigate, hard for various groups to locate the documents that they thought were most relevant to them. And we're in the process of having to address all of these things, because obviously, we need to make this communication form as efficient as we possibly can.

So I'll summarize this part of my talk just by saying that I believe the drug safety board and the advisory committees have separate vital roles in the way CDER responds to drug safety, and that we do have available venues that we put to good use to assure appropriate public input on safety decisions.

The second part of my talk is just a brief discussion and follow-up to what we talked about at our last meeting, which had to do with the priority setting for the drug safety board. There's a continued interest in the drug safety board in providing a focus on emerging drug safety issues and

how best to communicate them. And since the last Science Board meeting there have been 11 safety communications discussed with the drug safety board, either before or after they were posted, and I've listed four examples here. Each of them were places where obviously a new alert was placed, where it was deemed important to have a public communication either around a new black box, a new serious toxicity, a renal toxicity, or cardiac toxicity in the case of aprotinin, or of a marketing suspension in the case of the Technetium-99 labeled Nutrispec. The point is that the board has continued to give us very frank, very useful feedback about these communications forms so that we're able to adjust our policies, adjust how we do these things, make them most efficient, and the best that we possibly can.

The other focus, and I'd say the other focus that the board has settled on in the last couple of meetings, has really revolved around process development. Again, a good part of their goal is to help CDER develop its processes to best respond to drug safety, either in terms of how CDER manages drug

safety concerns internally, just working them through, making a regulatory conclusion, and how best to communicate things. And it's that former piece that the drug safety board has really taken on seriously, especially in the last few meetings. They've begun work with the CDER staff on how best to track these sorts of things within the center, and there have been a broad discussion about the needs for a CDER-wide tracking system for identified safety issues. That's an ongoing source of discussion for the board.

Additionally, they've recognized the need for looking back at and sort of making the process documents that we've been working on as good as we can. And if you remember, there is a guidance for the drug safety board. They have now made suggestions regarding how best to approach that guidance, and the comments that we've received, and we're in the process of revising that guidance, as well as a map, a document that will guide staff activity for the drug safety board, so Dr. Cummins and her staff, how best to handle the emerging safety information as it comes in and work them through the center. So, again, a

focus on the process to make certain that CDER is doing the safety issues as best we can.

This slide is just to highlight that, and what I've done is I've taken the list of bullets that we talked about at the last meeting, and where we asked about prioritization, if you remember. The two that are in red both relate to process, both relate to how CDER approaches drug safety and manages it in an ongoing fashion. I would say these are the things that the board is currently focusing a lot of their energies on, a place that they've sort of taken on as a task that they're planning on going forward, and so as far as priority setting, the board has really come to the place where they view this as a large part of what they need to be doing into the future. And I think it's something that CDER welcomes. It's going to be a very useful thing for us to help us hone our own process internally.

So I'll summarize this particular part just by saying that I believe the drug safety board continues to develop its role within CDER. It is continuing its role in assisting effective safety

communication. I think they've never failed to give very useful information as far as how best to communicate these things, how best to get things out to patients and healthcare practitioners.

More recently, they've taken on this interest in the focus on process development to make certain that the CDER processes internally are maximally efficient and best suited to address the safety needs. And I think I'll just end my part of this CDER feedback by saying, again, I strongly believe that the drug safety board does not replace or diminish the importance of advisory committee meetings, or reduce the discussions of safety in public venues. I believe the drug safety board continues to be a valued new voice to assist CDER decision-making on drug safety. And, Mr. Chairman, I'm optimistic. I think the development here has been very fruitful. I think we've made good progress. I'm looking forward to what the next years bring.

DR. SHINE: Thank you very much, doctor. Why don't you hold on, let's hear from Paul, and then we'll have a conversation about this.

DR. SELIGMAN: Thank you. Good morning, Mr. Chairman, members of the board. My voice has recovered since the last time I was here. I'm delighted. I have provided you all with a handout that really contains a fairly good description of some of the databases that we use in the post-marketing environment, AIRES, the drug utilization databases, our population databases, access to the general practice research database in Britain, and so I'm going to - yes, you don't have it. If you could take a moment and hand it around, that would be great. The reason being is that I really -- it contains sort of a lot of detail regarding the populations that are covered, et cetera. There we go. These are actually the slides for my talk. Okay. But the reason I want -- I'm not going to go through all these slides. It's just too much material, and I think I'm going to give you sort of an overview of what we do in this particular area, and then be prepared to answer any questions that you have about these specific databases.

The background and context, which is

summarized in my slides, I'm going to focus in large measure on the way we collect safety information in the pre-market environment. I think most of you understand and recognize the strengths and weaknesses of clinical trials, why clinical trials are conducted, and how safety information is garnered in this particular environment. I think the only thing I have to report in this regard is that we now have a guidance to industry on pre-market safety assessment that we issued a year ago March as part of our PADUFA agreements, which is there to guide industry and have them focus on key safety issues that need assessment in the context of the clinical development of a particular product, and to look at important data issues, particularly with regards to missing data and important analytic issues regarding how to handle and manage safety information that's derived from the clinical trial.

We also now within the CDER have a guidance to reviewers on how to do the safety assessment, how to organize that information and present it, and are now working on, I think, a number

of valuable and important analytic tools that will improve the way our medical officers and reviewers handle what is often a fairly large amount of safety information that is collected in the context of the clinical development of the product.

I think you all know this, and I don't need to cover this. What I did want to talk about briefly is that there really are six major ways in which we learn about the safety of products once a product is approved. One of them is under-appreciated, but is really a very important aspect of this, is the ongoing clinical development of a product. We still learn a lot about the safety of products from ongoing clinical trials, either for other indications that a sponsor is pursuing for the development of a particular product. We also learn a lot from Phase IV studies that were negotiated between the sponsors and the FDA to either evaluate either particular safety signals or important information. And then, as you know, we spend -- the tracking of adverse events continues to be an important aspect of the way we learn about new safety information.

Our focus in the adverse event reporting system has been to improve the way we receive these data. Over 50 percent now of the adverse events that are serious now come in electronically from sponsors, 33 percent of our overall adverse events now come in through electronic submissions, so improving the speed with which we get this information is important.

We have also now completed the development of a web visual data mining tool which is now in the hands of all of our post-marketing safety evaluators. They've all been trained on its use, and we anticipate in these coming months look at the way we handle our adverse event reporting data and the way we analyze these adverse events that this data mining tool will improve not only their efficiency, but also their ability to identify and detect signals in that database.

Also, as described in my handout, we have had and now have access to other drug utilization databases that we routinely access, not only to determine the degree to which products are being utilized, but what kinds of practitioners are

prescribing these drugs, but also gives us important information about how drugs are used concomitantly and in what combinations within practice.

We have four recently completed awards for population databases with Kaiser Permanente, Engenex, Harvard, and Vanderbilt. And again, the populations that are covered within these databases are described within my handout. And the solicitation and performance of population epi studies continues to have an important role in our ongoing assessment of not only the kinds of adverse events that occur, but also, in particular, risk factors associated with those adverse events. And finally, we monitor the scientific literature. And there is still a considerable amount of work that goes on independent of the FDA's - not only supported by other federal agencies, but also supported by industry and other institutions that occurs in the academic world, which continues to inform us about new adverse events, and new concerns related to drug safety that we continue to pay attention to.

In the Office of Drug Safety per se, its

role has expanded considerably in the last three years in the areas of safety beyond just the post-marketing assessment, to include close work with the clinical reviewers and understanding the safety profile of drugs in clinical trials, to try to anticipate the degree to which certain kinds of adverse events need to be monitored closely, and the degree to which there needs to be planning for pharmacovigilance in the post-marketing environment, to the development of risk minimization action plans.

Since 2002, the Office of Drug Safety has reviewed over 96 such plans, 15 of which were for new molecular entities during this particular time, as ways of working closely with sponsors to ensure that the medical community that prescribes these drugs not only understands the risks, but they are appropriately educated, as well as the patients are educated about the risks associated with these drugs.

So with that, I'm going to stop and turn it all over to you to basically ask questions. I know part of my reason for being here today was because there were, I think, questions from many of you and

part of the panel regarding what we're doing in the area of post-marketing safety, how we're monitoring adverse events, the degree to which we're using the latest or the best tools, and understanding the safety profile of drugs. So with that, I'm sort of here for the next 45 minutes. Okay. All right.

DR. SHINE: Thank you Dr. Seligman.

DR. SELIGMAN: Sure.

DR. SHINE: Questions for either of these two presentations? Dr. McNeil.

DR. McNEIL: I have a question. My memory may be wrong, and I'm not sure to whom I'm addressing it, you or to Doug. So it's the Nutrispec issue, and is that the one that failed in patients who had abnormal liver function tests, and therefore, the antibody got trapped in the lung instead of in the liver?

DR. THROCKMORTON: No, it was an imaging product, and there were reports of cardiovascular adverse events, collapse, hypotension and things like that very shortly after administration. We don't honestly know the exact nature of those.

DR. McNEIL: Idiosyncratic.

DR. THROCKMORTON: Yes.

DR. McNEIL: So it wasn't the drug that -- okay. I thought there was a drug that had just recently gotten taken off the market that was noted to specifically fail in patients who had abnormal liver function tests.

DR. THROCKMORTON: No, this one - we weren't able to identify a population like that. One of the things that we wanted - we obviously talked to the sponsor about and tried to do that. That wasn't something we could do.

DR. GALSON: Abnormal liver function tests or liver abnormalities are really the greatest cause of problems with drug safety, so there are other drugs that might fit that profile. But I don't know off-hand.

DR. McNEIL: Well, let me tell you what my general question was, and pretend there is such another drug. I thought it was this one. If that were the case, would that not have been found ahead of time in subset analyses, or in planned analyses from

the original Phase III clinical trial? Would those, going back to the original comments about power, would they not have been powered appropriately to find such an effect, or would have to go this sort of thing? Are they idiosyncratic?

DR. GALSON: I think a bunch of us could answer that, but sometimes yes, and sometimes no. It depends on the frequency of the events. We certainly have refined the way that we design clinical trials to pick up as much of this as possible, but sometimes, as you know, the number of patients that are involved in clinical trials, compared to the number of patients who take a drug when it's out on the market is minuscule, so there are events that are simply not predictable by the methods that we're using now. We're hoping in the future many of the projects that we're working on in Critical Path will enable us to be able to predict much better than we can now who will develop these. But right now, the methods are quite imperfect.

DR. McNEIL: So that's really the under-powering issue.

DR. WOODCOCK: Yes, if I could respond, too. We look at people with abnormal liver function and abnormal renal function prior to market for most drugs, so the metabolism or the disposition of drugs in people with impaired metabolism is examined. But that's different than an idiosyncratic reaction that might involve the liver, which we might not pick up, but might have no relationship to impaired liver metabolism, but that is examined. Now rarely, especially for an imaging agent, for example, you might not have that many people who have impaired liver metabolism. So if it's rare adverse event in people with impaired liver metabolism, you might still not find it. However, you do evaluate the levels in people with hepatic impairment prior to approval, so that there is knowledge about that before something gets on the market ordinarily.

DR. McNEIL: I guess my general question, and I think maybe you answered it at least in part is, to what extent now or in the future you need to be powering some of the clinical trials for more adverse events.

DR. WOODCOCK: Can I answer that? Paul, do you mind?

DR. SELIGMAN: And then I'll follow-on.

DR. WOODCOCK: Yes. You don't know in advance what the adverse effects are going to be. And unless you look for -- unless you design trials to find something specific, you may not find it anyway. Now overall, there are certain sizes of safety databases that are required pre-market. However, if an event, for example, is an increase in frequency of an event that is common in the treated population to start with, then you still may not pick it up, so the issue of power is not a very simple issue. What we are trying to do under Critical Path is to try to develop more mechanistic approaches to understanding -- some of these side effects are based on metabolism, for example, and the drugs currently are not dosed according to metabolic variations, so there is not a simple answer to this question.

DR. SELIGMAN: Yes. And just to add to that, in addition, clinical trials are really designed to sort of focus in on the degree to which a product

works, and it can't predict the co-morbidities, the co-prescribing, the complexity with which a product is going to be used --

DR. WOODCOCK: Or misused.

DR. SELIGMAN: -- or misused in the real world. And so sort of the sky is the limit. I mean, in large measure, after a product is approved, it's the real world laboratory that we're really interested in, in trying to keep a close eye on and monitor carefully.

DR. SHINE: Dr. Laurencin.

DR. LAURENCIN: The one question is, the advisory committees make recommendations and then FDA staff act upon those. The drug safety board votes, they make recommendations for staff, or they actually, since they are staff, they actually vote on these rulings. How does that work?

DR. SELIGMAN: They can vote internally, but their role is to advise the Director of the Center for Drugs.

DR. LAURENCIN: All right. And then he makes the decision based upon their recommendation.

DR. THROCKMORTON: He makes the decision based on a series of recommendations. The board is one place that such recommendation could come from, one important place when you're talking about drug safety.

DR. LAURENCIN: This was established as a result of a number of things last year. Does it have a term limit? Is it permanent? What's the plan?

DR. SELIGMAN: I don't believe there's a sunset to the board.

DR. THROCKMORTON: Well, some parts of the board were proposed - the drug watch and things like was proposed. We put this out as a response to drug safety. Right now we're in the process of looking back at the comments we've received about this. We're talking internally about it, but I believe, Steven, you're sitting here. You can say for yourself. I think this is a useful voice for the center; but, obviously, it at some point became less useful or something. I guess Steven would be --

DR. GALSON: There's no plans to sunset it; although, like other procedures in the center,

we're going to change it if it's clear that it's not working, and we can think of ways to improve it, including the membership, so it's not fixed in stone at all. We've already made changes to it.

DR. SHINE: Dr. Roses.

DR. ROSES: Since decisions are made using data that comes into the MedWatch database, and much of that is through voluntary reporting, what is the thoughts about how to validate the data that comes in so that the decisions that are being made are based on such data?

DR. SELIGMAN: There are really two approaches. One is, clearly when we're looking at the potential of taking a regulatory action based on these data, we spend a lot of time looking at the cases and getting more information, and ensuring that they're high quality cases, and that we have a careful and thorough assessment that gives us some confidence regarding the relationship between the drug use and the adverse event. As you might suspect, and actually as you probably already know, a lot of these cases are complex, they're confounded. They're often very

difficult to interpret.

The fundamental weakness of the adverse event database, of course, is that it contains no denominator, and we are always sort of searching for the true rate of disease, and whether what we're observing here is comparable to what might be observed in sort of the background population for the adverse event of interest.

One of the areas that we're clearly very interested in is active surveillance, the degree to which we can use population databases like United Health Group, or Kaiser, or Harvard, for the elderly hopefully the Medicare Part D data, the degree to which we can use the information about prescribing and outcomes in databases to verify or validate the degree to which what we may have observed as a case report or a series of case reports is being observed in other settings. I think we're still in our sort of earliest phases of that effort, but it clearly needs to be done.

We are acutely aware of the kinds of pressures that lead to adverse event reporting, and

the contexts in which people do or sometimes do not report to us, and so we always look at these reports not only thoroughly and carefully, but with a clear recognition that there are lots of reasons that influence both the number, as well as the quality of reports that we get.

DR. ROSES: As a follow-on, what would be the prospects of being able to take a series of very serious reports that you would consider actionable of itself or in aggregate to obtain test materials from the patients involved, so that more accuracy and more science could be developed about those patients and those adverse events?

DR. SELIGMAN: Actually, Janet might want to discuss the way this -- what we've been actively engaged in in talking with folks at NIH and others about ways in which we can use potential case material, or case reports and potential materials that might exist that could be used to further identify sort of the underlying basis for why an adverse event occurred in an individual or individuals. Clearly, there's a lot of interest around hepato toxicity,

around cardio toxicity, around renal toxicity where, indeed, these case reports might be a fertile substrate for doing further science to figure out what's going on behind those cases.

DR. SHINE: Do you want to comment, Janet?

DR. WOODCOCK: Certainly. This is one of the things that was mentioned in the Critical Path report. And I think only in the past few years - Allen, you may dispute this - but really only in the past few years to my belief, have we really developed the scientific tools that we're really going to be able to do this. But we are going to do this, because people don't just randomly have these adverse events. There is a reason they get them, and either they are having drug interactions, they're having metabolic differences, metabolism differences, or they have pre-existing conditions of one sort or another, pre-existing biological predisposition, for example, to having an adverse event. And we are working with a wide variety of people, and we're going to figure out ways that we can actually get the science done to track this down, get medicine up to -- safety medicine

up to a whole new level of understanding.

DR. SHINE: Let me ask a couple of questions. I think Dr. CASSELL also has some questions. First of all, what's the size or magnitude of the population that you currently are able to survey through the Kaiser, Harvard, Vanderbilt activities, what are we talking about?

DR. GALSON: Tens of millions of people.

DR. SELIGMAN: Yes, it's tens of millions. I have to -- the HMO Research Network has 3.2 million covered lives, Vanderbilt has 2.2, Kaiser is 6.1, and Engenex 12, so it's about 20 million, roughly.

DR. SHINE: Oh, I see. Okay. There is some data in here in the handout.

DR. SELIGMAN: Yes, 20-25 million.

DR. SHINE: And if you were to get access to Medicare Part D, then your population would be --

DR. SELIGMAN: Bigger.

DR. SHINE: Like what?

DR. SELIGMAN: Oh, gosh. I'm embarrassed I don't know the number, but I'd be willing to guess 30-40 million range. Does anybody know what it is?

DR. McNEIL: I thought it was 20-25 million.

DR. SELIGMAN: Twenty to twenty-five, okay.

DR. GALSON: Let me just point out with that, there is no such thing as "access to Medicare Part D" at this point. The data systems are just being developed. It's not like --

DR. SHINE: I understand.

DR. GALSON: We can't sit down and type it in and get an answer.

DR. SHINE: Yes. But you are working on that, so you would, in fact, have access to another 20-25 million.

DR. SELIGMAN: Right. And for CMS, the real issue is going to be marrying the prescription data with the Part B data.

DR. SHINE: And as soon as the elderly population figures that out, you'll be able to do that.

DR. SELIGMAN: Right. Well, that's another matter. Right.

DR. SHINE: MedWatch provides a voluntary reporting system.

DR. SELIGMAN: Correct.

DR. SHINE: Are there other ways that information comes into the FDA with regard to adverse events? I guess the fundamental question is, how complete is your collection of the adverse events that you may become aware of in other parts of the organization? And the corollary to that is, as I understand this, these are drug events. What about other kinds of biologic and others where there's an adverse event, what happens with those?

DR. SELIGMAN: Well, the biologic events that are associated with other biologic drug products we get into our system.

DR. SHINE: Okay.

DR. SELIGMAN: There is a separate vaccine adverse event reporting system that collects exclusively vaccine reports. The first part of your question has been the conundrum that has faced us for a long time, which is how complete are our data. We just, to be honest with you, other than some work that

was done almost two decades ago, we just don't have a real good sense the degree to which these data either do or do not represent, or the degree to which they represent a complete ascertainment of adverse events. We know that they don't. Whether it's 1 percent, 10 percent, or 33 percent of all that's occurring out in the world, we just simply don't have a handle on.

DR. SHINE: Well, I understand that you're not going to know about the ones in the outside world. My question relates to what is all of the information made available to the FDA through any sources, does it get into your database?

DR. SELIGMAN: Well, when manufacturers see those reports, we're pretty confident that in the vast majority of cases, they are sending it to us. We have a means of actually physically auditing manufacturers through our compliance and field divisions, and one of the things that they do on field inspection is go out and look at the case reports that are in their files. And in preparation for those inspections, they will actually ask us what have you seen from Company A in the last three months or six

months, and so they're able to compare what they're finding in the files versus what's submitted to us. And there are occasions, of course, when there are discrepancies, and there have been occasions where there have been serious discrepancies. But I would say for the most part, I'm confident that, at least on the manufacturing side and those who have requirements to report to us, that they adhere fairly scrupulously to our reporting requirements.

DR. SHINE: Dr. Cassell.

DR. CASSELL: I just wondered in your current system, do you know how good you're capturing data in terms of adverse reactions in the pediatric population? And of the new networks, Vanderbilt, Harvard, et cetera, do you know percent of those would, again, be pediatric patients versus others? And the reason I'm asking this is that we heard a few days ago at the IOM about a Children's Health Network that's being established through some professional societies and so forth, that sounds like it could be a very good model for adverse event reporting and other things. And the second part of the question is that

we also had a workshop that dealt with the role of consumer in adverse event reporting, with the idea that pharmacists should be playing a much more active role, perhaps, in educating patients in terms of what adverse reactions to anticipate, and then reporting back. And I wonder is FDA taking a proactive role in trying to promote that with regards to the pharmacists and their role, or is any group, as far as you know?

DR. SELIGMAN: Okay. Well, let me take the first one first, then the second one. Regarding pediatrics, all three of our databases, Kaiser, Engenex, and Harvard are HMO networks that clearly cover wide populations, so they give us to the degree that adverse events are occurring in the pediatric population, we're getting those reports.

One of the nice things about the Vanderbilt is that it covers the Medicaid population. And, as you know, Medicaid covers a fairly substantial portion of children certainly in the jurisdiction in Tennessee where they're doing their work. We're always interested in trying to look at other networks that might provide us information.

There is a drug-induced liver injury network that we've been working with for many years. We currently have a relationship with the CDC and the National Electronic Injury Surveillance System to do adverse event vigilance within the 64 hospitals to see what is coming in through emergency departments, so there are, I'm sure, many ways in which we can use networks to enhance our ability to collect information. And the one you suggest may turn out to be one we should pursue further.

Now give me a word about your second --

DR. CASSELL: The need to better educate patients on potential adverse reactions.

DR. SELIGMAN: And pharmacists.

DR. CASSELL: And the the role of the pharmacy.

DR. SELIGMAN: Right. One of the things, there is current legislation and rulemaking at the FDA which will put the MedWatch number on all the amber vials that are distributed in prescriptions, so we're not entirely sure yet what the impact of that will be, but if and when that occurs, it will certainly raise

the profile of our MedWatch program, and the ability and awareness of consumers to use that as a potentially reporting vehicle for adverse event reports.

In the area of drugs, actually pharmacists, particularly in hospitals, turn out to be the leading reporters directly to our MedWatch system. Although I've never seen any direct survey evidence, I suspect that in certain contexts, pharmacists may be more aware of the MedWatch program than other health professionals, and they do submit usually very thorough and high quality reports to us.

There is some work being done in the private sector about ways in which we can better engage pharmacists both in the education of patients and consumers regarding adverse events, but also ways in which pharmacies and pharmacy networks can be used to actually collect some of this adverse event data. I know the CPATH Institute is doing something of that nature in Arizona at present.

DR. SHINE: Yes.

DR. PI-SUNYER: Do you do any sharing of

data with other agencies outside of the United States, like the British Health Service, or some other systems that are also doing surveillance?

DR. SELIGMAN: Yes. Actually, our adverse event data goes to the World Health Organization and becomes part of their larger database. We also are part of an international program called VigiMed, which is a vigilance system that allows sort of email interaction and interchange of adverse events in countries all over the world where individuals have questions. And I monitor that myself, actually. We get about half a dozen queries a day from countries all over the world - have you seen this adverse event? Is this drug being used in your particular country? What's your experience?

And finally, we have a regular interaction, a video conference with the European Medicines Authority where we share information and talk about topics of interest, as well as an additional teleconference with the Canadians, the Australians, and the New Zealanders over the same kinds of topics, what are you observing your arena,

sharing cases.

We also have with the AMA a confidentiality agreement which actually allows us to share with them fairly detailed information about case reports should it be necessary.

DR. SHINE: This is a question more for Doug. Doug, you've made a good case for the functions of the board versus the advisory committees. There still is a certain amount of discomfort about the board in terms of the issue of public input, things of this sort. There are ethicists at the NIH, and I would raise the question of whether you would not consider a government employee ethicist as part of that activity to give the perspective of somebody who's not a regulator, but is somebody who could give input in terms of the risk benefit kinds of issues, and ask those kinds of questions on behalf of the public. Where are we with regard to names and packaging? Have we made progress with regard to decreasing the number of patients with similar names and similar packages?

DR. SELIGMAN: Boy, what a question.

DR. THROCKMORTON: Paul, why don't you let me do - I'll do the first one, and then you can frame the answer to the second one, because it's a very complicated topic. We've not said -- we've had an ethicist as necessary, something we'd absolutely look to. We actually have ethicists on staff at the agency level, as well, and within the FDA, has helped in a large number of areas for CDER. And so, whether or not there's the need for a standing ethicist to be on the committee, I guess that's a larger conversation. Certainly, as an issue arose that needed to have ethical input, we've said --

DR. SHINE: But that's not what the ethicist does for you. The ethicist sitting there listening to all of these things raises questions that you may not even have thought about. That's the purpose of having an ethicist there. It's not -- if it's something you have to bring in an ethicist on, of course, you use them, but I'm arguing that having somebody there - it's like having a female on a search committee. You'd be surprised how often they will not scratch women off the list if there's a woman on the

search committee. Anyway, it's just a thought. I'm not trying to belabor it. But I am interested in this issue of labeling.

DR. SELIGMAN: Dr. Shine, I need to send you the USP poster of the 600 product combination names in the United States that are currently marketed that have similar sounding names.

DR. SHINE: I'm talking about new products.

DR. SELIGMAN: New products, right.

DR. SHINE: What are we doing about when new drugs are approved?

DR. SELIGMAN: We still review every single one of those names, and we put them through a three-stage process. One is, we now have analytic software called "The Phonographic and Orthographic Computerized Analytic System" that actually takes each name and compares it both in terms of its length, the number of letters, its syllables, as well as phonetics, and compares it to all existing drug products in the United States, so that's the first cut that we do. And then we take the names and we do sort

of an internal experiment, which is we actually have our doctors write these prescriptions. So we're still doing that review, and we're still picking up names and rejecting them.

DR. SHINE: Okay. So you are rejecting names that are too similar. You are looking at packaging in terms of not confusing --

DR. PARKINSON: As a beneficiary of that process, I can tell you, names are being rejected constantly.

DR. SELIGMAN: I don't know if this is progress or this is good. We rejected about a third of the names submitted to us last year.

DR. SHINE: Okay. I'm reassured.

DR. THROCKMORTON: And we're also in the process of writing sort of best practices document to tell industry more about how we're making these sorts of decisions, so that it's not -- it's never been capricious, but I think we need to be able to explain it as clear as we can, and that's not yet available, but that is something else that's going on.

DR. SHINE: One last question, and then

Dr. Von Eschenbach has a comment to make. You made reference to responding to public comments on the part of the board. You have a website. People make public comments through the website? How else does the public get a chance to, not in the advisory committee sense, but in the safety board - how do they get a chance to get their concerns to the board?

DR. THROCKMORTON: Concerns regarding the board, or concerning --

DR. SHINE: Concerning a product.

DR. GALSON: I would say on that, as you know from the presentation, the board is an internal management board --

DR. SHINE: I agree.

DR. GALSON: -- for the center. There are lots of ways that we collect information from the public when they're concerned about drug safety. We have an 800 number, and when calls come into that number, they get distributed out to the people that can most handle them. If they get turned into AIRES reports, that's one thing. If people have questions about a product, they go somewhere else, so I think we

have a fairly robust, probably not enough, outreach with the public.

DR. SHINE: But how does the board find out about those? Does the board know that the public is terribly concerned about XYZ?

DR. GALSON: Yes. I don't think we've established that particular connection, because we hear about 10,000 products every month, and so if that's what the board was going to take up, what is the public concerned about at this moment, that's all they would do.

DR. SHINE: No.

DR. GALSON: Yes.

DR. SHINE: The question is, what is the public concern about an item that the board plans to consider. You have a limited agenda in terms of those drugs that you're going to be looking at.

DR. GALSON: Let me give you an example of something that we're currently getting a fair amount of public comment about, which is the Tysabri, the decision that's being made. That's a thing that we're receiving a lot of public input about, appropriately.

It's a complex issue, it's a complex decision. The way we've been routing that has been through, again, the people that deal with the external relations people, but they've been focusing on sending those things to the division and the places actually making the decisions. In that regard, it's sort of most important that those things are heard by the people ultimately making those regulatory decisions. The board hasn't been a part of that.

Now to the extent that any of those offices viewed the comments that came as raising a safety thing, a thing that the drug safety board might well consider, then the expectation of the center is that they would bring that to the board. They'd say we want to discuss this.

DR. SHINE: Commissioner, you're the only thing remaining between us and lunch. Would you care to make some comments? Oh, I'm sorry. There is another question here, but why don't you go ahead, Dr. Von Eschenbach.

DR. VON ESCHENBACH: Go ahead.

DR. SHINE: Dr. Harlander.

DR. HARLANDER: I guess this is more of a philosophical question, but as I listen to all you're doing to collect adverse reports that might warrant taking a drug off of the market, how do you assess the risk of not taking it off the market? I mean, I think there's -- I guess it gets to your risk benefit question, and that has to be a hard one because if there aren't any alternative drugs available for an individual, and is there a threshold level of reports that would say it warrants taking a drug off of the market? I mean, how does the board deal with those kinds of issues, because personally, I may want to have the choice of taking that risk, but that's kind of taken out of my hands by --

DR. SELIGMAN: Well, you've already hinted at the complexity of how those decisions are made, and it's a combination of both science and data, as well as, I guess you described it as philosophy, which is, is this a unique product? Are there other alternatives? How do you value choice versus not having access to a particular product? I mean, at the end of the day when a product has worked its way

through clinical trials, we know that, if it's approved that it works. And most of the reasons that products are withdrawn is because that sort of risk balance equation seems to have tipped in the other direction. It's one of the reasons why we're looking so carefully at ways to effectively manage those risks to ensure that those who would most benefit from the product will continue to have access to it, and for those for whom it may be a risk, that we try to limit or prevent them from getting the product. But there is no easy, or magic formula, or equation, or algorithm that we can apply to each product, and each circumstance is a different one.

DR. SHINE: And, of course, this relates to why products have warnings, black boxes, or whatever, that there is still a benefit, but a significant risk. Dr. Laurencin.

DR. LAURENCIN: I went over your slides, and there's one slide I just can't read, maybe because I've reached that 40 plus age where the eyeballs change.

DR. SELIGMAN: No, I've got the same

problem.

DR. LAURENCIN: It's slide number 9.

DR. SELIGMAN: Okay. Let me go right to it. Oh, yes. Okay. I'm sorry about that.

DR. LAURENCIN: What is this?

DR. SELIGMAN: This is the trend in adverse event reports from the early 90s through to 2005. Simply to show that there's been a dramatic increase in the number of reports. We've been getting, particularly in this last decade, about increasing by 10 percent from the previous year of reports. We're now getting about 450,000 reports a year.

DR. LAURENCIN: You've doubled over the last three years.

DR. SELIGMAN: That's correct.

DR. LAURENCIN: And what are the green, yellow --

DR. SELIGMAN: Actually, the most important one is this sort of magenta one, which is the number of serious adverse events that are being reported to us, just to emphasize that we're making a

really concerted effort in terms of reporting in trying to get those reports that have either led to death or disability, or hospitalization, or considered to be life threatening.

DR. LAURENCIN: Now the drill down of this is that the number has doubled over the last three years because of reporting, and that's the only reason?

DR. SELIGMAN: Yes, we don't know why it's doubled, other than that -- well, we actually have a few clues. One, electronic reporting has meant that we're getting a lot more of the non-periodic reports entered directly into our system. There's some data that we used not to enter into our adverse event system, but there's also more drug and drug products out there. One could speculate as to what accounts for this rise, and I --

DR. LAURENCIN: The yellow is what?

DR. SELIGMAN: Yellow are what we call periodic reports. They're the non-serious reports.

DR. LAURENCIN: And the other one is?

DR. SELIGMAN: You're talking about the

turquoise one. Turquoise is non-serious periodic, I'm sorry about this. Tell you what, I apologize.

DR. SHINE: Why don't you print a good copy?

DR. SELIGMAN: I will print you a good copy with not only a clear index, an explanation of what those various bars are.

DR. SHINE: Thank you very much.

DR. SELIGMAN: Okay. Sorry about that.

DR. SHINE: Obviously, there's more drugs and they're also more potent, which makes a difference. But in any case, Dr. Von Eschenbach.

DR. VON ESCHENBACH: Thank you, Mr. Chairman. I wanted to take the opportunity from the Commissioner's perspective to just piggyback on the question that Gail raised having to do with the pharmacy, and address the larger systems approach to this issue of drug safety.

This morning when we were talking about research, we talked a lot about integration, and we talked about, Mr. Chairman, your concepts of the fact we've moved out of a reductionist approach and into a

systems biology approach. And I think it's important for the board for me to emphasize the fact that from the agency's perspective, from my perspective, we're really looking at this drug safety issue as a systems problem that needs a systems solution. And the point that Gail raised with regard to so what's happening in the pharmacy, I think some of the things that we have done in the integration of those pieces really hope to be a more comprehensive solution.

For example, the physician's drug label, the changes that were made there, the fact that now that label is able to be updated electronically on an ongoing basis - that that information is then, because of information technologies, will be readily available at the point of sale, if you will, at the pharmacy using some methodologies that could enable the pharmacist to print out the summary statement, that then provides to the patients an up-to-date understanding and appreciation of what things to look out for. And then to be able to have the system through information technologies and even putting on the bottle how they could get that information back in

to us to close that loop, so that it really starts to become a systems way of being able to make sure that we are identifying what those risks might be, communicating them effectively in as broad a way as possible, having means of being able to get sensors and information, and inputs back in to us to inform the constant evolution of this, I think is the kind of approach that we are going to be consistently taking across the whole variety of these issues and concerns.

I wanted the board to know that as you are looking at the parts and pieces, where also you're going to be consistently hearing from me the drive for integration, the drive for being able to make sure that we're putting all these parts and pieces together in a way that gets us the effects that we want, which is a much better system.

DR. SHINE: And this is consistent with the notion that healthcare in general has to be approached as a systems problem, in terms of quality of care, and the whole way we operate. We have the largest cottage industry in the world, we have some of the biggest cottages around with very fancy

technology, but we do not have a system of care, so this is an important contribution to make to that.

We will adjourn for lunch. We will resume promptly at 1:00. We have a number of committee members who have airplanes to make, and we want to be certain that we get our business done this afternoon, so let's take a break for lunch. Thank you.

(Whereupon, the proceedings went off the record at 11:54:23 a.m. and went back on the record at 1:05:36 p.m.)

DR. DHRUVAKUMAR: I do not have any financial relationships with any entities that may be affected by the outcome of this meeting. My name is Sadhana Dhruvakumar. I'm a scientist at PETA. I'm the Director of Medical Testing Issues, and I'll be speaking to you today about drug safety, animal use, and Critical Path Opportunities.

The latest Critical Path Opportunities report contains a statement that, "It is important that we strengthen our post-marketing surveillance of adverse events, but our ultimate goal should be to prevent adverse events from occurring in the first

place. We need to build safety into products from the ground up." But when you look at the current way we build products, most of R&D and safety, preclinical safety and efficacy testing is conducted in animals, so the basis of our human medical products, the foundation of them is animal research, and that isn't the best way to build safety for humans into products, as we can see from the fact that 92 percent of drugs that go through preclinical testing and work in animals -- work and are safe in animals -- now fail during the clinical trial phase.

We had a very public recent example of that with the recent tragedy in the UK, where six men suffered multi organ failure and lapsed into comas based on a monoclonal antibody Phase I trial, so this example has really drawn the public's attention to the fact that even though these products were tested on monkeys, these effects were not seen, and animal tests do not necessarily predict human results. As the BBC News put it, "Animal tests can be a false reassurance." Obviously, this type of adverse event is relatively rare, this degree of adverse events.

However, we do know that quite often the animal tests do not predict various types of adverse events in humans.

Another example is Vioxx, which, of course, is linked to numerous cardiac deaths once on the market, but even Merck in studying the animal models, while admitting that the relevance of the animal models was not clear to humans, they found that the results raised the possibility that COX-2 inhibitors could actually decrease the incidence of acute thrombocitic events, so not only do the animal models not predict the human problem, but they actually predicted the opposite. This was highlighted by testimony from the former Director of Cardiovascular Medicine at the Cooper Clinic in Dallas, Dr. John Pippin, both in Congressional testimony and at an FDA hearing. And also, there's a lawsuit based on the fact that Merck did not protect people by basing its safety results on monkey results.

Turning back to the Critical Path, the original White Paper in March of 2004 had numerous instances of pointing out that problems with animal

toxicology and animal testing, animal toxicology may fail to predict the safety problem that ultimately halts development. Animal models may not reflect the real disease state, and across the board the current way that we do drug discovery is fundamentally unable to identify candidates with a high probability of effectiveness. So the solution -- we've been waiting for the solution.

The Critical Path Opportunities List has come out. Across the board it is an excellent document, but with respect to its treatment of animals and use of animals, the report has many opportunities that call for new animal models. It calls for improving extrapolation from animals to humans, and also the biomarker work is currently focused on animal biomarkers of toxicity, which only improve our ability to predict animal toxicity. They may or may not be able to make that leap across to humans. And as previously pointed out, animal toxicology may be unpredictive of humans, so there is not as much of a focus on calling for new human tissue models, calling for new really innovative technology, such as the bio

chips that I presented to you, such as the hurel at the last meeting. So in listening to Dr. Von Eschenbach's talk, he said a couple of things that really resonated with the point that I wanted to make here.

He talked about the fact that science and healthcare research has moved from the macroscopic to the microscopic, to the molecular. And many of these animal models were created at a time when the view was macroscopic and/or microscopic, but if that was the only thing that people understood to do then, that was the reason they came about. But currently, what we really need to focus on is, as he said, not only the disease, but the human who gets the disease, and we can't study that in a rat.

He drew an analogy between the future of medicine being like a butterfly that is unrelated to the past, which is like a caterpillar, so basically I felt that he was talking about a paradigm shift, that we need to really just move away from these old models and really focus on what is going to be the future, which I believe will be, if we think about the future,

it will be based on really high tech next generation human relevant models, and trying to promote incremental improvements in basically flawed model of animal surrogacy is like trying to put a dress on a caterpillar instead of focusing on what that butterfly is and how we can get there quicker.

I wanted to talk about an example of a transition from an animal to a human relevant test, which is stuck. And I spoke to you last time about rabies vaccine potency testing. In the meantime, I have met with the rabies experts at CBER and it became painfully clear through that meeting that the very reason that this animal test, which is highly variable, more than 400 percent variability is common, painful and widely criticized test cannot be replaced because it is so inconsistent, that a better test that was created only a couple of decades later now for 30 years has not been able to replace it. This kind of situation should not happen. There's a problem when something like this is going on. The better test is not currently being used by regulators or industry across the world because of this problem, so this is

due to the limitations of the entrenched animal test, and also of the regulatory response.

Another thing that I learned from CBER is that the FDA does not have the ability, if there are two tests, does not have the ability to require the company to use the better test. They have to accept any test that shows the safety, so even when better and advanced models come out, companies often cling to what they know, and the FDA has no power to require them to use what is ultimately a better and more protective test for humans. And I heard the same thing from Center for Devices in a meeting yesterday, so I think that's another problem that's arisen.

So I would like to suggest that an effort be undertaken to identify the top worst lab safety tests. They don't have to be animal based, but I believe that if we looked at that, we would find that they were rabies potency -- I talked to you last time, as well, about carcinogenicity testing, which has similarly been criticized, widely criticized for about 25 or 30 years, and has never been -- people just keep criticizing it, but no one actually instigates a

replacement or something that would fix the problem.

Basically, I think these tests that are truly just reviled, it would be pretty easy to identify them by surveying stakeholders and looking at data that the FDA holds, and basically create a collaborative, or prioritize an effort to replace these very worst tests. There tends to be a trend, it tends to be that these things are only addressed when a tragedy occurs. The NIH test, so far, hasn't resulted in a wide scale tragedy; thus, it is considered acceptable, even though we know that it's highly variable and untrustworthy. For example, with the egg-based production of vaccines, as well. People knew for decades that that was a very outdated technology that didn't make any sense, but there was no priority to replace it until there was a very public scandal around a flu vaccine. So basically, trying to be a bit more proactive about these things, and really identify the worst offenders, and solve those problems that people just talk about, but no one takes the initiative to solve.

The ways that this could happen, I

suggest, could be a science board review. This could fall within the domain of various FDA bodies, or the Critical Path Initiative could address something like this. There could be a new FDA division. I think that would be the best solution, tasked with assessing the quality of the preclinical tests that we use, both validating new tests, and also invalidating these old tests.

And that brings me to my final point that I wanted to raise. Another problem that I see with the agency being able to move from old test methods and old science to new ones is in this process of test method validation. Basically, because there is no real forum for that to happen, new methods get held up at that point, and they cannot make it into the regulatory books, and into use, so we end up with test methods that are 70, 80 years old still being used.

The Inter-Agency Coordinating Committee on the Validation of Alternative Methods is an inter-government body which is meant to address cross-agency methods, but in fact, they keep recently getting methods that are FDA-specific, such as pyrogenicity

testing and Botox testing because these are submitted by outside bodies who, in one case at least, tried to go to the FDA and ask about this, but there's no real place for this to happen at the FDA, so it's inappropriately going to a cross-agency body.

Following from that, when novel tests are validated by these bodies, such as ICCVAM or its European counterpoint, ECVAM, there is no clear process for incorporating that into FDA regulations. FDA is a participant in ICCVAM. FDA will often write a letter in response to some of the things that ICCVAM does, and maybe put out a *Federal Register* notice, but in terms of changing the CFR, changing the guidelines, and especially when things happen at ECVAM, they don't necessarily translate into any improvement or change in the FDA. And so in reading about the predictive safety testing consortium where the pharmaceutical companies are working together pooling their data on animal toxicity biomarkers, and with the help of the CPATH Institute working as kind of the venue for that to happen, for that data sharing to happen, and also, they're working in their labs to do inter-laboratory

validations of each other's biomarkers, I felt that this construct could be one place where this could lead to validation of novel test methods; not just biomarkers, but if there's a new human skin model, if there's a new -- other types of things where you can do safety testing, then this could be one mechanism. But others could exist, but I feel that this is a real gap that's keeping science from progressing at the FDA. Thank you for your attention.

DR. SHINE: Thank you very much. We have a copy of your Power Point as part of the record. Do we have any other testimony?

DR. JOHANNESSEN: Not that I know of.

DR. SHINE: Okay. Thank you very much.

DR. DHRUVAKUMAR: Thank you.

DR. SHINE: We'll move on to the response with regard to the peer review of the pesticide program. For those who are new to the Science Board, an internal review was done by ORA. Their conclusions were then subject to review by a panel, which included Kathy Swanson and John Thomas who is -- Kathy is still a member of the board. John was previously a member

of the board, plus a number of ad hoc members. That group made a report at our last meeting, and we're now looking for the Regulatory Affairs Pesticide Program to respond to that review. Who is going first, is Carl? Please, go right ahead.

DR. SCIACCHITANO: Thank you very much for us to give a presentation, update on the pesticide review. Especially, recommendations from the external purview on pesticide program. Within the Office of Regulatory Affairs, my division, the Division of Field Science oversees the pesticide program for the field activities, and with me here today is also Dr. Steve Robbs who handles that for us, and he's been involved tremendously with the board going through this process.

What I want to do is look over the observations, the recommendations that you've made, and show you the progress we've made to-date. First and foremost, I'd like to mention the collaboration, and Bob will address this, as well. The collaboration we have with the Office of Regulatory Affairs and CFSAN. It's been a very effective and productive

initiative. Much of the buzz words we heard this morning about integration, synergy, and such, is clearly seen in the implementation of procedures. Most importantly is the composition of these groups. Not only it's the scientific part with the Division of Field Science, Office Enforcement, Import Operations Policy, Investigations, and in CFSAN and Contingency, as well, to look at these issues.

What I have done is grouped some of these observations together, just to give more context and meaning behind them. And for the first three observations, really dictate to the pesticide program design. And we have the handout, so I won't go through each one, but critically looking at a risk-based approach, CFSAN Senior Management and ORA are looking at developing a risk-based approach to many things, not just the pesticide program but looking how this can improve our regulatory decision making, functions and operations, and pesticides clearly is under that umbrella.

From the status standpoint looking at all resources, how we can obtain information to promote

better quality, better program, looking at outside resources, pesticide violations, mentioned eLEXNET, the Electronic Laboratory Exchange Network. This is something to consider. Within eLEXNET, you have approximately 122 laboratories that have some capacity of entering data into a system, and this comprises the federal level, the state level, and the local level. There's a lot of information out there that we need to assess, a data mine. We can't ignore USDA/AMS PDP program, and other types of state data, as well.

For observation four, a couple of points, and this is more or less the implementation side of the house. And the comment here or the observation was a lack of coordination between sample collection and analysis. The external review committee noticed a lack of communication between the laboratories and the collection districts. And since then, we've gone through a process of identifying this issue, and something we're calling the National Sample Distributor. And I'm going to explain how this would work. It's a national type initiative where usually laboratories would obtain samples from a collecting

district. Well, the National Sample Distributor would identify the capacity of a laboratory; so, for instance, if we're dealing with the Northeast Regional laboratory, and they claim, and I'll just pick a number, 30 samples a week they can do. Okay. The National Sample Distributor would identify that, and when they fill that quota of 30 samples per week, again, the next laboratory in line would receive those samples, so it would be a balanced flow of sample distribution through the field laboratories. More or less looking at the field laboratory as a national entity versus silos, and dealing with one laboratory. But my interest not only is the balanced sample flow that this could accommodate, but clearly identifying also laboratory capacity, and that's difficult when we're looking at defining laboratory capacity, establishing criteria to do that.

Arbitrarily, one can pick 30 samples per week, but is that accurate? What is the maximum they can do in a most efficient way, most productive, and looking at time frame issues. So these are things that we're looking forward to as far as we roll out

the National Sample Distributor. Plans are a pilot in August. I'm not sure which region, either Southwest or Pacific we're going to start it looking at a pilot, looking at lessons learned, and then upon its success, and I'm very optimistic because it will, looking at it from a national standpoint, so this is one major initiative that we're going to be doing.

The second thing to address communication is re-establishing the pesticide coordination teams within each region. Apparently, this fell by the wayside. They're being restructured. They're redrafting the field management directive to establish this, looking at the correct composition of the pesticide coordination team and looking how not only from the sample flow and distribution, but identifying local issues within each region in each district to make sure those issues are being resolved, and those samples are targeted, and the right analyses are conducted.

The other on the method issue is the pesticide analytical manual, and also a method validation protocol needs to be developed. Give you

status on both of those. Pesticide Steering Committee has been formed, again looking at, and it's redundant but it's important to emphasize the composition of these type of committees to include users, to include the researchers, experts in the field, and the centers.

The Pesticide Steering Committee also functions as editorial board of the PAM. Clearly, we need to look at new efficient methodologies, pesticide methodologies that are being developed, and also implemented in the field labs. We need to make this an evolving process, not a static process with the PAM and keep it up-to-date.

The other issue, observation seven was method used to analyze samples, maybe not comprehensive. And this issue, again, I'll talk about it in a second, but basically we're talking about some pesticides that might be not detected by current methods. That's what I'm talking about being more comprehensive.

To deal with these type of issues, I can just tell you from the Office of Regulatory Affairs'

perspective, a unique perspective that the field labs bring to this process is the validation of methods. This clearly can't be missed when we're talking about research, or any type of method development. Before implementation into a field laboratory, there are certain criteria that need to be met. The commodities that we look at are tremendous. If you for one second think a method can be applied to all foods, that's erroneous. It's impossible. And with quality assurance and laboratory accreditation issues, it's even more important to show that validation data to support those commodities. We established for the new Office of Regulatory Affairs a method validation development program. Many of these method issues from the research developed at the centers, but particularly CFSAN in this case would queue into a method validation program to make sure we had that validation data to support those methods. So in line with prioritization initiatives for the centers and also with ORA users and their needs, as well.

Observation eight dealt with no tolerance pesticides, and we'll deal with this. To deal with

these issues of non-tolerance, the steering committee is looking to revising the criteria for animal packages. And just recently with our field food committee, met a couple of weeks ago, we formed a sub-working group to again identify the issues, better define and apply the import appearance standard. We need to streamline the process, look at the significance, the magnitude of the testing we do, and also make sure we're looking at all the legality issues, making sure that the impact of the changes are congruent with the needs we have.

Uniform procedures for capturing, sharing, reporting, auditing raw data are lacking. Over a year ago we had a contract to look at the laboratories and basically do an assessment of what type of laboratory information management system we need, or what it would look like, the cost. That was completed and that's being assessed. Also have what's called MARCS. It's a merging platform for strategic systems, and see how we can incorporate IT management systems within MARCS. These things are being considered under IT umbrella, and again, streamlining the process and

meeting that objective.

And lastly, observation ten, quality assurance programs are inconsistent across ORA laboratories. Now I think since the peer review, I'm not sure what the status was at the time, but since then three laboratories have been accredited, Arkansas Regional Lab, Pacific Regional Lab Northwest, and the Northeast Regional Laboratory. And as you can see, the Pacific Regional Lab Southwest and the Kansas City Laboratory will have accreditation confirmed by May 2006, and the Southeast Regional Lab in June 2006. But here's my -- it's again my opinion, again accreditation is a significant event. Maintaining accreditation is probably harder. And I say that because we need to standardize a uniform standard operating procedures, and the way I describe it to the laboratories is we have common SOPs. We need to do the same thing. The bifurcation might be the specialty of the laboratories, but from a common denominator, we need to work on looking at the pesticide program, look at what we can work on together, harmonize approaches, and accreditation is a

great platform to do that, and we continue to do that. So that's a quick update, and I know Bob wants to -- before I go to Bob - John, did you want any comments?

MR. MARZILLI: No, Carl. I just wanted to say thank you very much to the Science Board, because previous to coming to Norris' shop, I was in the Office of Regulatory Affairs and headed up the project here. And I think it really dovetails well with Dr. Von Eschenbach's talk this morning, and I think the leadership of John Thomas and Katie from the Science Board really helped us to take a program in our field organization that was stovepiped, and really take it across the field, and bring it together as a cohesive program. And I think with Carl's leadership as the new Director of Field Science, and you'll hear from Bob in a bit from the Center for Food Safety, I think we're off to a good start with this program, and it will serve as a boilerplate I think for many programs in the FDA field labs. I just wanted to thank the Science Board.

DR. SHINE: Before we go to Bob, I misspoke. John Thomas is still a member of the board,

it's just that he isn't here today. He's lost a lot of weight. Kathy, what's your response to this response?

DR. SWANSON: Well, first of all I'd like to thank you for responding to the report. When you put in the amount of time and effort into coming up with recommendations and then not knowing whether or not it was implemented I think leaves us in a vacuum. But you took the effort to let us know what is going on, I think that's very important.

Working on the lab capacity, I think is a great step forward. That was one of the things that the entire group thought would be very beneficial, and so compliment you on that. The PAM update, I'm a microbiologist and I know the BAM, but the folks that we're working on the pesticides were very passionate about the need to update the PAM, but the validation of the methodologies in, and so I think that the response is right on track.

I would hope that at least a copy of the presentation could be sent to Joanne Cook and Mark Lee, and Steve Musser so that they would be aware that

the fruits of their efforts -- as well as John, of course, but they're not on the science board, so that they know that the fruits of their labors are seeing some advance.

DR. SHINE: Okay. Any other comments for Carl? Carl, I would find it helpful if on a number of these issue you benchmark the time that you are going to complete the task. For example, on revising the PAM, when do you expect that to be done? There are a number of issues that I think sometimes benchmarking it in terms of some goals is a good way to assure that it gets done in a timely way. And I would urge folks in responding to reviews to do that kind of benchmarking. We don't need to see that. I would think at the time that you send out the material to the other folks, the addition of those benchmarks would be constructive.

DR. SCIACCHITANO: Sure, that's great.

DR. SHINE: Should we go to Bob? Thank you, Carl.

DR. BUCHANAN: Having enough familiarity with this board and as I start looking at the door as

the afternoon starts to tick by, I decided not to use slides, but I did want to reinforce and augment some of the things that Carl said. And I'd like to express CFSAN's appreciation for all the hard work that went into this evaluation. It provided a very insightful report, and I want to just reinforce, I've been working with various boards now for almost 10 years since it was originally formed, and I want to reinforce that we do listen to these reports, and actually make substantial changes in our programs as a result of it.

I also want to emphasize that this was an interesting one because this is one of the first reviews that actually spanned multiple centers. And this has been very helpful in improving CFSAN's interactions with ORA. The report was very insightful and very helpful in identifying for us areas where our lines of communication had built up a lot of static, and provided us a means with helping us filter out that static so that we could start listening to each other again. And I think that Carl's mention of the pesticide steering committee is an example of where

that is a result that has already started to improve those lines of communication.

We do very much appreciate the encouragement of the board on further refining our program so it is better risk-based and statistically based. I know within the center we've already started to deal with this by revisiting our definition of high risk foods. I might note here that this is a very important definition because this determines what is going to be the focus of our request for surveillance activities every year, so that definition is critical to this. And we're also using this to go back and further enhance our traditional risk focus in this arena on foods that are eaten in large quantities by children, and trying to focus that down even more.

Taking advantage of and working with ORA to take better advantage of our historical data that we generate, taking advantage of better infrastructure for determining and taking the right samples at the right time, and certainly we've started to do a great deal of thinking particularly in conjunction not with the pesticide program only, but also with our food

defense program on how to take the right sample, how do you take a smarter sample, not more of them?

I might note along that line the improvements we're going to see in these areas, particularly in risk-based and statistically-based if we're restricted to taking more samples, is going to be a difficult one considering the resource limitations we have to increase any of our sampling programs, so we're going to have to take smarter samples.

I might note we also have to maintain a flexibility within that program so that we can continue to use this not just as a means of determining what the baseline is in the country, but this program is also used as a deterrent, and we need to fully appreciate the deterrent nature of the samples we take that are not necessarily statistically-based, but are there to encourage people to comply.

Your comment on reinvigorating the analytical manual joins a number of different voices from different stakeholder groups that we've received

about the importance of our analytical manuals, not just to our own operation, but also to the world in general. And I might note that both of our major guidance documents on analytical methods, the PAM and the BAM for pesticides and for microbiology have had their stakeholder -- their editorial boards reconstituted, and we're in the process of putting out new revisions of both of them.

Pam Makovi has agreed to take over as the editor of the PAM, and has now put together a team of both CFSAN and ORA personnel to start updating the PAM. And Keith Lampel has taken over the operation of the BAM or the Bacteriological Analytical Manual. And again, it is in a new revision.

Now I do challenge the board here - we're not going to provide you a date on when that's going to be done, because hopefully it will never be done. That's why we got ourselves into the situation now with the PAM, as somebody said, we're done. What we will be happy to do is provide you a date with the next revision.

DR. SHINE: Fair enough.

MR. MARZILLI: Okay. We are in total agreement with your comments on being able to continually improve the effectiveness and cost-efficiency of our analytical capabilities. We put a great deal of effort in trying to find both more sensitive and more cost-effective methods, and being able to increase our throughput, something that is particularly a challenge when you're talking about resource limitations.

We think that CFSAN, and CFSAN has promised to work closely with the pesticide steering committee, particularly on our role to identify critical research needs, improve approaches to validation, and also enhance our ability to transfer the technology in a useful manner out to the field.

We do appreciate you taking on the question of no tolerance pesticides, and it pointed out, again, one of those areas where static had built up in our lines of communication, that we had to better communicate to the ORA the implications of not quantifying samples, such as this, in terms of our obligations and commitments under the World Trade

Organization treaty. And the fact that we do need some minimal amount of quantitation so that we can met the requirements of those treaties. We have established those and that communication is now starting to pay off, so that we understand and can come up with as simple a way as we can of dealing with this issue.

And then finally, I'm going to lump the last couple of observations together and say that CFSAN has re-again made a re-commitment to working with ORA to provide them with the help they need in terms of the information and data technologies that they need, the accreditation of their laboratories. And again, I think that I can say that this is an area we're going to work as diligently as we can within the resource constraints that we currently have in terms of our field force and our laboratory commitments.

I might also note that this has also become critically important as we use this data not only for determining the safety of individual lots of food, but using that as is part required, as part of our evaluation of the functioning of this system. The

new requirements of the Information Quality Act that we now all have to live under make the ability to look at those data sets and have high degrees of confidence in them an absolute mandatory part of our activities.

And so finally, I'd like to, again, express CFSAN's appreciation for the hard work that was put in on this evaluation, and then reinforce that we have read it, we have listened to it, and we are actively trying to find solutions for it. And with that, I'd be happy to answer any questions.

DR. SHINE: Thank you, Dr. Buchanan. Any questions? Kathy, questions?

DR. SWANSON: No, not really at this time, but I'm glad you're putting it to use.

DR. BUCHANAN: Okay.

DR. SHINE: Bob, I was pleased to see about the lab accreditation that Carl pointed out. I do think that implicit in that was the notion of trying to get a fairly uniform Quality Assurance Program across the labs. That's not necessarily a trivial undertaking, and I could see being accredited in a variety of levels of quality assurance, so I hope

that you and Carl will look very closely as that accreditation process goes forward and is rationalized so that there is a consistency in terms of the quality assurance methodologies.

DR. BUCHANAN: And I might note, that that's an issue not only for our regulatory labs, but that's an issue with our own research labs. I do have to also indicate that I know that we have to have accreditation by multiple agencies and multiple groups now, and it is becoming a major activity for us in terms of resources. By the time you deal with the accreditation for good laboratory practices, our own internal QA program, working with ORA on accreditation issues, our animal care and use accreditation, we're talking about a fairly hefty activity for us at a time --

DR. SHINE: Sounds like a medical school dean. Thank you very much. Bob and Carl, please express our appreciations to your colleagues for the cooperation they showed in the review. I want to express, again, our thanks to the review committee, and I hope, Jan, when the summary of the response to

review is sent, that you'll accompany that with a thank you note to the people who did a nice job with regard to this, and we look forward to continued progress with regard to these programs. Thank you very much.

If there's no further comments, we'll move on to the CVM NARMS Program. This is another example of a program that involves multiple entities, in this case the Food and Drug Administration, the Department of Agriculture and the CDC. You should have received a book. I hope you all had a chance to read it carefully. Submitted by the Internal Review Committee. We've got a brief update with regard to that report, and I'm charged with appointing a small committee to conduct a similar review to that which we just heard about in ORA. And, Steve, you're going to -- yes.

DR. SUNDLOF: I'm going to kick things off. Thank you. And I want to thank the Science Board because this is a very important issue for us. If the Science Board hadn't been available, we would have had to basically have gotten another body to

review this, because this, as Dr. Shine pointed out, this involves more than one agency. There's a lot of public interest in how NARMS is operated and the results that come out of NARMS. And because of that, we think that after 10 years, it really deserves a good outside look. So, again, we really appreciate the fact that the board is willing to do this.

NARMS is really a program that was born out of necessity to address a very important regulatory problem for the FDA. Antimicrobial resistance and the role that agricultural use of antibiotics plays in that has been the subject of intense debate since the 1950s, and until 10 years ago there wasn't a lot of resolution, but the debate was becoming huge. And what we realized, in fact, people that were a lot smarter than me realized that rather than relying on a few published literature reports, which seemed to make a correlation between animal agricultural use of antibiotics and human health problems -- there really wasn't much for a regulatory program to go on, and we really needed something permanent in place to give us an ongoing survey of

what was happening both in the animal world and the human world, and whether or not there could be correlations between that use of antimicrobials in animals and the transfer of those to humans. And what would be the impact, public health impact of that. So NARMS was created. Again, it does involve the human community from CDC standpoint, looking at human food borne infections, and whether or not those organisms causing those infections are resistant to antimicrobials. It also involves an animal portion, which is the jurisdiction of both USDA sampling animals at slaughter and determining what human pathogens may be resistant to a battery of various antibiotics. And also, looking at retail meat, going around and surveying meat from the retail counters, and determining, again, what humans might be exposed to in terms of antimicrobial resistance. And so that is the program that you are going to be evaluating.

One of the issues that keeps coming up, and that is that just to avoid any mischaracterization. Most people when they think of this issue immediately think of using antibiotics in

feed to improve animal growth rate. And although that's part of this, it's not the whole thing. We want you to examine the total role of antibiotics used in animal agriculture, both for animal health purposes, and for other sub-therapeutic purposes.

Just as an aside, and before I introduce Dr. White, we are also involved in a risk assessment on food safety aspects of cloned animals. And as part of that exercise, we did some focus groups asking people what they thought about cloned animals. But our first questions to them were well, tell us what you think about food safety? When we say food safety, what does that mean to you as a consumer? And they immediately almost to a person said antibiotics and hormones in food. That's the thing that people care about. And so it is an issue that has a lot of public interest. We take it very seriously, and so I'm going to ask Dave White to come up and introduce the internal review to you.

Dr. White is the Director of NARMS in CVM, and he received his Master's Degree in microbiology from the University of Kentucky, and his Ph.D. in

Veterinary Science and Pathology at Pennsylvania State University. And he also served as a post doc under Dr. Stewart Levy, who many of you in the field know as one of the pioneers in antimicrobial resistance. So with that, Dave.

DR. WHITE: Good afternoon. I'd like to thank you, as well, for taking your time to come on a Friday afternoon, and of course, in a few hours braving the traffic in this Rockville area. If you've not done it, it's going to be a challenge.

As was mentioned, I think you've all got the packets. This was put together by the internal review committee, and I'd like to take about the next 15 minutes to provide the background on the planned peer review process that we look forward to you participating in.

Some background, as Dr. Sundlof mentioned, in food animals, of course, antimicrobials are used for the control, prevention, and treatment of infectious bacterial diseases, as well as for enhancing growth and feed efficiency purposes. Unfortunately, an undesired consequence of this use is

the potential development of antimicrobial resistant zoonotic bacterial pathogens and subsequent transmission to humans. Recognizing this potential health hazard, it's become a global issue, of course.

WHO, FAO, and OIE have recommended that countries implement monitoring programs aimed at determining the occurrence of resistance in bacteria from animals, foods, and humans. So with regards to NARMS, as Dr. Sundlof mentioned, it's been in existence about 10 years. It was actually created on the basis of a Veterinary Medical Advisory Committee with Fluoroquinolones back in 1995, 1994. It was one of the recommendations of the Veterinary Medical Advisory Committee, if you're going to approve Fluoroquinolones, you needed a monitoring program in place, so that's how NARMS came to be.

As was mentioned, it's a collaboration between FDA, CDC and USDA, as well as public health laboratories in all 50 states, and also local health departments in three major cities, so it's a very large network. It's grown tremendously in the past several years.

As I mentioned, it was developed to monitor changes in susceptibility resistance of select zoonotic bacterial pathogens, primarily Campylobacter and Salmonella. But over the past several years, we've added commensal organisms as sentinels of resistance, in particular, generic E. coli, as well as Enterococcus, trying to monitor those resistant phenotypes. And we monitor them to a panel of antimicrobials of human and veterinary significance, ones that would be used to treat, of course, enteric infections in humans, as well as in animals.

And as we mentioned, the three testing sites are the Office of Research at the Center for Veterinary Medicine in Lowell, Maryland. That's where the retail meat and poultry testing is conducted. That's headed up by Dr. Pat McDermott in the Office of Research. CDC, which is, of course, Atlanta, Georgia. That's headed by Dr. Tom Chiller, and USDA is in Athens, Georgia, headed up by Dr. Paula Fedorka-Cray.

The goals are very broad in terms of the program. One is to generate descriptive data on the extent and temporal trends of antimicrobial

susceptibility resistance in enteric organisms from human and animal populations. Also, to provide information to veterinarians, physicians, stakeholders, and public health authorities on emerging, unusual, or high levels of bacterial drug resistance so that timely action can be taken to protect public health.

Also at NARMS, we are able to design follow-up epidemiological and research studies to better understand the emergence and transfer of drug resistance. And ultimately, to prolong the life span of approved antimicrobials by promoting prudent judicious use of these compounds.

In terms of the reviews, we've had two reviews in the past several years with the program. On August 12th to the 13th, 2003, CDC conducted an external review of solely their part of the program, and that's actually reported in Appendix One of the notebook that you received. We also last year on June 23rd to the 24th had an expert review, where we invited in several individuals with expertise in epidemiology and microbiology to solicit individual opinions on the

program. This focused on all three arms of the program, and the results of that expert review are provided in Appendix Two in the booklet you were given.

With regards to this committee today, we created a NARMS internal review committee, and it was charged with conducting a self-assessment and preparing recommendations for the science board. It was made up of multiple members from the Center for Veterinary Medicine, as well as for CDER, Office of the Commissioner, USDA, and CDC. And once the committee started meeting, we identified four areas where we thought the science board could contribute to a review of the program. One is sampling issues, second is epidemiological and microbiological research, third is harmonization of data reporting, and lastly, coordination with other international surveillance efforts around the world.

We feel that NARMS is a very strong program, and is an important part of national public health surveillance in the U.S. It has broad support from diverse sectors and numerous stakeholders. As

Dr. Sundlof mentioned, it has matured since its inception in 1996, and we feel the benefit from the input of the FDA science board on its key elements in future directions.

So in terms of the information that was provided to you, it contains background and information with regards to the four key areas we'd like your input on. As I mentioned, sampling, epidemiological and microbiological research, harmonization of data reporting, and coordination with international surveillance. Each of those four sections is structured the same way with an introduction, a description, relevant comments from the CDC external review, relevant comments from the expert review, strengths and limitations from the internal review committee, as well as recommendations on where the program needs to go.

There is also five appendices. Appendix One, as I mentioned, is the CDC external review and their responses back to that review. Appendix Two is the FDA/CVM expert review. Appendix Three is the NARMS internal review committee members. Appendix

Four is publications that have been put out through the various NARMS components over the years. And Appendix Five is examples of tables and figures or NARMS' integrated report where we're moving to this year to create an executive summary, which we have not done before. So that's one of our major goals for 2006.

We've also provided relevant background information, one on the CAHFSE Program. This is out of USDA. It stands for the Collaboration for Animal Health, Food Safety, and Epidemiology, as well as information on FoodNet, Guidance 152 which is one of our guidances on how antimicrobials are looked at, when we evaluate the safety with regards to human health concerns, and the presentations from NARMS scientists back in June, 2005.

We came up with four questions that we'd like you to address. One, are there inherent biases in the sampling strategies employed in NARMS? If so, how can they be improved to ensure that the data and our interpretations are scientifically sound, given current resources. Second question, are there

epidemiological and/or microbiological research studies that would better serve the goals of NARMS and the regulatory work of FDA? Thirdly, are our current plans for data harmonization and reporting appropriate? And if not, what alternative approaches would you consider, and what should be the top priorities for harmonization and reporting? And the last question, are the current NARMS international activities adequate to maintain a significant collaboration with worldwide efforts to mitigate this threat of antimicrobial resistant food borne bacteria?

With that, I'd like to recognize the contributions of the members of the internal review team. Like yourselves, they wear many hats, and I appreciate the time they took to look at this internal review process and come together with these recommendations to you. That's all I have, so I'll entertain any questions you might have.

DR. SHINE: Questions for Dr. White. David, in terms -- I was trying to rationalize the questions you're asking with issues that came out as far as the CDC's review is concerned. They look like

they're very similar.

DR. WHITE: Very similar, absolutely.

DR. SHINE: What are the nuances? Are there some things that we should be recognizing as different, or a perspective that would be --

DR. WHITE: Yes, that's a good point, and what I'll point out is that the CDC one was just on their part of the program.

DR. SHINE: I understand.

DR. WHITE: We need more input on the retail and the animal arm, as well as improvements that CDC has undertaken since that review, and to see if that satisfies the needs of the program. They're very similar to what has already been addressed in the expert reviews.

DR. SHINE: Dr. King, I don't know how much you've had a chance to look at the NARMS material, but as one of our bona fide veterinary medicine people who's also spent time at the CDC, do these look to you like the right questions that we should be addressing for this program?

DR. KING: Yes, I think they really are.

One of the questions I had was what's happening internationally? Is there a convergence of what's going on in terms of expanding the database, taking samples, something like salmsev. That's a WHO, could other organisms be used and kind of have you thought about that? That's part, I think, in your questioning, and I know that's what CDC has in mind, so that's one question. And then I think the other is, just kind of your take on having three different groups working on this. From your point of view, are there other better ways to collaborate, or communicate these results amongst the three?

DR. WHITE: Thank you. That's a good question. With regards to the first question - what was it again?

DR. KING: Salmsev.

DR. WHITE: Salmserv, international activities. Thank you, Dr. King. Sorry. My sister is in labor right now. I'm waiting for a phone call to let me know that she's given birth to my god-daughter, god-child, and it's been a long labor. She's been in labor --

DR. SHINE: Well, it's going to be a niece or a nephew, or something of that sort. What is this God business?

DR. WHITE: There you go. Friday afternoon. My niece, thank you, sorry. The international activities we feel is very important, and we were at actually the international conference on Emerging Infectious Diseases last week, where we attended the GSS meeting. And CVM actually contributes quite a bit of money to that program, as well as NARMS people for training, so that's one of the programs we do support in terms of global initiatives.

We've also been collaborating with folks in Denmark with Denmap, CIPARS which is the Canadian Integrated Program on antimicrobial resistant surveillance. We're starting to do more interactions with them on the North America surveillance, as well as we funded a program in Mexico to develop a NARMS similar system called ResistVac. So once that's all done, we're going to have surveillance systems that are communicating between Canada, United States and

Mexico, so it's really going to be a nice North American type of surveillance system. So that's what we're trying to do. And then, of course, once we get North America straightened out, then start expanding out internationally.

As you know, for those of you involved in surveillance, there's probably at least 25 different surveillance programs like NARMS around the world. Japan has one, Denmark has one, Sweden has one, Norway has one, France has one, Spain has one, Italy has one. I think one thing we're trying to do is to unite those at some point. And Dr. Chiller at CDC, that's one of his goals with this. In your book it's called INSAR, Integrated Surveillance for Antimicrobial Resistance. We hope in the next several years to try to put together a meeting, of course, we don't know who will fund it, but to try to bring all the programs together to start talking. Because what happens in the past, and what we've had to do with NARMS, is we've had to harmonize even the methods used within the NARMS laboratories, is what we use for susceptibility testing methods here in the States is

not maybe what's used in Spain, or in England, so that's a big step that we'll have to do. It's going to take some time.

Secondly, in terms of working with the three agencies, my position is fairly new. I've only been in this position about four months. Before that, I was retail meat team leader. It's been some bumps in the roads over time with three different agencies working on this program, but we're all pretty committed. We all met last week down at ICID again, and we all are committed to converging on one road, so to speak. And that's what an example would be this executive summary that we are tasked to put together by the end of the year. We're going to highlight data from all three arms and certain tables that makes it very explicit on what's happening between animal retail, so I think we're making progress. Does that help? Yes.

DR. HARLANDER: Can I ask where and how are your results communicated? Like how am I going to find out about what the result of this is?

DR. WHITE: Sure, good question. We have

three websites, there's a NARMS website that's hosted at CVM, that if you do a Google search or Yahoo search, just type in NARMS and you'll get the NARMS main web page at FDA. In that main page, there's NARMS retail data reports, CDC human reports, and the animal arm reports, as well.

The one thing we're trying to work on with this executive summary is each one of those reports can be up to 400 pages, so what we need to do is to pull out important information from those three into one document that people can read. They're very extensive. We've done every type of permutation possible because we have so many different stakeholders. We have industry, we have public health people, we have the states that are participating as well, so every permutation that can be done with the data is there either in a table, a figure, or appendix. Does that help? We also publish --

DR. HARLANDER: I would encourage an executive summary, because I don't think most of us are going to plough throw 400 pages for each arm.

DR. WHITE: And that's one of the

recommendations that's come out previously, and we're moving on that. We also publish papers on NARMS, that if you do a search and search under NARMS, there's several papers. We always present at international meetings. We had 12 posters at ICID on NARMS from the three arms, so we're really well represented. What we need to do is to start having posters and presentations on all three together, because what we've had in the past is a NARMS retail poster, a NARMS animal poster, a NARMS human poster, but not one that pulls all the data together, which is where they're going.

DR. SHINE: Dr. Swanson.

DR. SWANSON: I think integration of the data, as you discussed, is absolutely vital. It's obvious that this work is important, consumer concern, medical concerns regarding increase of antimicrobial resistance, so I applaud that, and think it's very important.

The one thing when I read things like this is I'm always looking at other ways to use the data. On the food safety side, antimicrobial resistance is

important, but there's also discussion about what is the influence of the level of these organisms on the intervention strategy, such as heat processing or other types of treatments. And it occurred to me that gee, if you're going through the effort of collecting the samples, how much extra work would it take to just do the analysis to try to do quantification, as well? It would really assist in worldwide efforts on new frameworks for food safety management where you need estimates of the initial population to be able to calculate what level do you have to achieve, so I know in a world of shrinking resources that saying here's one more thing you could do is usually not welcome. But a lot of the effort is just in going out and getting the samples, so I thought I would just toss that out.

DR. WHITE: That's a good point. We've been thinking the same thing. Unfortunately, with the retail meats we're up to 5,000 meats, so you're talking quantifying, and these are done at the state laboratories. And they're already overwhelmed with the other functions that they serve, but we do

coordinate with CFSAN and FSIS. And FSIS is about to start whole new bunch of baseline studies where they will quantify, so we're working with them. We share prevalence data with them so they can get indication of what we're seeing in NARMS, and that's one of our goals, as well, is to integrate within other agencies that have public health as their focus, so that's something we're trying to do, too.

DR. SHINE: Dr. King.

DR. KING: One other question, I think what we may find is that we'll have better problem identification as we learn more. One of the things that at least I saw in a micro level in my college is people coming in and talking about the judicious use of antibiotics, and it's made quite an impression on our veterinary students, and they're doing the same thing with medical students, so it's one thing to further identify the problems. This is studying getting back into prevention, and awareness of young professional students that have made really an impact, and so as they go out and are making decisions, I think it's been very helpful. So one of the questions

might actually be in the prevention area, in terms of what else can be done. But I was impressed with that.

DR. WHITE: Thank you. We actually have summer interns that come in, and we have veterinary students that come to our laboratories, as well, and learn about NARMS, and we send them back. We try to interact with AVMA as much as we can. Up until this past year, we used to have NARMS meetings in terms of a half-day session on food safety. I don't think we had one this year because it's in Hawaii, but next year it's in D.C., and I think we've put forward another one. And that's where get a hold of the veterinarians. We also give talks at the specific, like the swine veterinarians, bovine practitioners and so forth, so we do interact with veterinarians, as well, in the different disciplines.

DR. SHINE: As you might guess, Dr. King is going to be one of the science board participants.

DR. WHITE: We welcome that. That would be very good. We work a lot with Michigan State, so that's a good thing.

DR. SHINE: Last, I have a very naive

question.

DR. WHITE: Yes.

DR. SHINE: I'm fascinated by the identification of the four classes of organisms you look at. And I'm just curious, are there other organisms which, perhaps, are less frequent, so they don't deserve this kind of surveillance, which turn up as a consequence of antibiotic resistance?

DR. WHITE: Oh, sure, plenty.

DR. SHINE: Like what?

DR. WHITE: Well, there's vibrious, listeria, I mean --

DR. SHINE: Those are the two that are mentioned in the report. They occur with a frequency or a prevalence that's low enough so that it's --

DR. WHITE: They're actually pilot studies, and they're only done by CDC. We don't have them in the retail meat portion. USDA doesn't do it either. That's part of the other obligations of CDC, is they get into listeria and vibrisis from the state public health laboratories. But for those organisms, as well, I think we have to design standardized

testing methodologies, as well.

DR. SHINE: And other organisms, what --

DR. WHITE: Well, in terms of zoonotic food borne enteric diseases, I think Campylobacter or Salmonella, E. coli 157, but that gets into a whole other jurisdictional issue. That's really FSIS and the zero tolerance with that. And the way 157, if I understand the pathogenesis is, we're not really concerned with antimicrobial resistance in that, because antimicrobials actually increase toxin production, if I remember, shiga toxin production, so they don't treat with antimicrobials with 157. Besides that, Yersinia is a possibility. There's a call for information on Yersinia enterocolitica, which we could certainly add. Again, it's resources. What can we do, what's the most we can do for the --

DR. SHINE: No, I understand. Thank you very much.

DR. WHITE: You're welcome. Thank you.

DR. SHINE: Our last presentation for the day is an overview of the Office of Women's Health. Kathleen Uhl is the Director of that office, and she's

going to tell us a little bit about it, and hopefully have a conversation about what kinds of things we might think about that would be helpful so far as that office is concerned. Dr. Uhl.

DR. UHL: Thank you very much, Dr. Shine, and thank you to all of you for kind of sticking with us. It's been a long two days, I'm sure, and I appreciate the opportunity to come here and tell you a little bit about the Office of Women's Health.

Okay. Now I was told not to be redundant, and not to bore you, so I will try my best on both. I thought it would be useful to just give you a little bit of the historical context of our office, why we were created, what some of our Congressional mandates are, and our budgeting, just so you have an idea of more or less why we're doing some of the things that we're doing. Provide you with a little bit of information about our staffing, and then get into some of the program areas that our office is involved with. So our office was established in 1994 by Congressional mandate. And at that time, the office was budgeted at $2 million. And what Congress mandated us to do was

to work to correct gender disparities in FDA drug device and biologic testing, as well as issues on regulation and policy surrounding women's health.

We were supposed to oversee the implementation of revised clinical trial guidelines with respect to the representation of women and the inclusion of women in clinical studies. And the last mandate, which is the one I call playing nicely in the sandbox, was to work with all the other offices or centers, or whatever that had anything to do with women's health throughout the department. And our budget has slowly increased from the $2 million to currently $4 million, and with those increases has also come additional Congressional mandates. So here are a few of the other mandates that we have, and some of the earmarks that go with them.

We have a demographic data initiative which I'll talk about a little bit later at an earmark of half a million dollars. The office was tasked following the first public release of WHI data, the office was tasked to put together a patient consumer information outreach initiative on menopausal hormone

therapy, and has had Congressional mandates in two consecutive years to work on that. And then lastly, we have a mandate on cardiovascular disease, which has even in Congressional language, the mandate of research, data analysis, and outreach activities to the tune of a quarter of a million dollars.

Our mission is to protect and advance the health of women through policy, science and outreach, and to advocate for the inclusion of women in clinical trials, and then also the analysis of women and sex and gender in clinical trials, so it's important to have women in studies, but also to go the subsequent step to analyze.

Our office is located in the Office of the Commissioner, as Dr. Alderson told you earlier today. And we serve as an advisor to the Commissioner, and we are asked to consult by the centers on a variety of different issues, different product issues or women health issues. We serve as an avenue for some of the women's health advocacy groups to gain access to the agency, so my phone and my email ring with incoming from women advocacy groups on a daily basis, wanting

information or wanting to know who they should speak with, how do they find out about information on such-and-such. But I think it's important to recognize that our office has no regulatory authority, and that's fairly similar to what the Office of Research on Women's Health at NIH has, parallel structure. They have no grant authority at NIH. They were created in `91, we were created in `94. Both residing in the office levels of either the Director or the Commissioner, so our office does not conduct reviews on products. We do not have the authority to approve products. Our office has 14 full-time staff members. We currently have two vacancies. Unfortunately, both of them are in our science program. We have two fellows, and our staff are allocated across, our outreach program has four staff, as you can see there. I have recently combined our demographic program and our science program under the same umbrella of a research and development program. There are administrative staff, specialized staff. These are two individuals, one of which has regulatory expertise. She served as project manager in one of

the centers, and I also have a medical officer, and then there's myself. And three of our staff members are also commissioner core, myself and two others.

And maybe a little distinction between our office and some of the centers, there was an issue discussed earlier this morning about budgeting and how much of the expenses are actually able to be used for program issues. And it's obvious that the bulk of the monies that most of the centers have goes to pay salaries, so in our case, about 30 percent of our monies go to pay salaries, so we actually have money with which to have programs with.

These are two of our programs. One is the outreach and the other is this research and development program. Our outreach program is geared almost exclusively to consumers. This is information about FDA regulated products at a fourth grade to sixth grade reading level, and we use partnerships with medical organizations, church-based groups, Fortune 500 companies, to really help get these types of messages out. And this is also another thing, Dr. Von Eschenbach talked about that this morning,

leveraging, developing partnerships, leveraging the limited monies that the FDA has. And this portion of OWH has really done an extraordinary job of that. They use these partners to develop the materials, to test the materials, and also more importantly, to disseminate the materials. All of our materials are available in English and Spanish. The hormone therapy campaign is available now in about 20 languages.

This is an example of some of our external partners. And I think what's most compelling on this slide, though, is it shows the aspect of leveraging. And here basically, these multitude of partners, as I said this is just a handful, they spend about $11 for every dollar that we spend, and basically, the use their monies to take our developed materials and publish them and distribute them to their members. And you can see across out partners here the diversity. There are medical professional organizations, Fortune 500 companies, lay magazines, church-based organizations, grocery stores, et cetera. So this program has really worked hard to develop many partners across a broad spectrum.

One of the big initiatives that the office did was this Take Time to Care Initiative, which the basic premise of this was to tell women to take time to care about themselves. And the cornerstone of this initiative was a safe medications use initiative, where what was developed for patients was a small brochure which actually was what I would have loved my patients to show up in clinic with, akin to an index card that provided them with space to write down the drugs they were taking, the doses, and the frequency. Nothing better than a patient who walks in with the medications they're taking, and that was the cornerstone of this initiative. This has evolved over time to include many different types of FDA regulated products. And you can see here that this Take Time to Care Initiative, all these underlined and bolded are some of the topic areas that they have addressed. And the partners that we've used to push out this message are chain drug stores, Dear Abby put something in her column a couple of years ago that ended up with solicitation at the Federal Clearing House that basically shut it down. The Conference of Mayors

partnered with our office on a breast cancer initiative. Blue Cross and Blue Shield used our cardiovascular and menopause information, and so this is a prime example of using someone else's dollars to distribute information.

CMS used the medication cards that I was talking about and distributed them to their Medicare beneficiaries. We worked with NCI with mammography information, and this is the most recent collaboration is with the North American Menopause Society to help distribute the materials on our menopause hormone therapy campaign.

Very briefly, this is a breakdown of our budget from last fiscal year, a little less than a million dollars dedicated to outreach, broken down into cardiovascular disease, menopause, and our core outreach issues which include breast cancer, diabetes, health fraud, safe medication use, and a variety of information about FDA regulated products.

Now I'm going to shift gears a little bit and talk about the research and development program, the first of which is this demographic data

initiative. This was a Congressional mandate in 2002, and the mandate told the office that what we needed to do was create a database focused on women's health activities to include demographic data in clinical trials. Now the initiative to-date has worked on trying to develop what is called DIDR, demographic information and data repository. This is an extensive IT management, knowledge management system that would potentially bridge all of the centers, and would allow the agency to electronically gain access across products, across centers, and whatnot, to be able to provide information about the inclusion of women in studies.

Now this is an extensive, if you can just try and envision everything electronically at your fingertips, where what we have now electronically at our fingertips often are PDF files of submissions, not searchable, not analyzable. We know how hard it is to try and create a database from PDF files, so what this would potentially be is a huge repository that includes basically all studies submitted to the agency, all applications, all reviews done by the

agency, and all labels. And this, to a tune of half a million dollars, is obviously some large disconnect, so the office has worked with CDER, Center for Drugs, on the development of a electronic review template with the intent of following good review practices, one very small component to eventually be able to create an entire electronic bioinformatic system like Janet alluded to a little bit earlier today.

Now what we are doing this year is just trying to get some data. What are the numbers, what do we know about the inclusion of women in studies? And right now we are in the process of reviewing submissions to our office from the human product centers providing us, hopefully, with information about the inclusion of women in either specific disease categories, or specific therapeutic areas. And the intent here is to be able to have some numbers. However, the five-year period that this DIDR has been funded, it has really been designed and working on the IT structure and the electronic aspect. I'm a little concerned that we've not generated any numbers, and that's why we're really focusing on some

data this year.

It's obvious to me looking at the submissions that we've seen so far, that it's a natural progression to partner the tracking of women in clinical studies with more scientific agenda. And an obvious way to link tracking of women with other types of analyses, efficacy, safety, genomics, et cetera, so in my mind, it's a natural progression to partner this demographic with the science.

Now our science program provides a foundation for developing sound policies and regulations to enhance women's health. Now our science program needs to be aligned with multiple priorities. We need to be aligned with the department, with the agency, with Critical Path, with the centers, with the offices, with emerging women's health issues, as well as the Congressional mandates that we have, so not an easy task. And to that extent, what I am doing is creating a women's health advisory council internally in the agency to help identify those priorities and bring them to our attention so we know which are the topic areas we

should be focusing on.

The science program selects projects, though, that will have regulatory merit, those that will eventually have some kind of regulatory impact or some regulatory implications. I do have a slide a little later to show you what I mean by that. The goals of our program are to address the gaps in current scientific knowledge around women's health or around sex and gender analyses, to encourage new directions in research, and to set new standards of excellence in women's health. And our program is broken down into basically three areas, an intramural funding mechanism, an extramural mechanism, and a special funding initiative. So our program has awarded a little more than $14 million since 1994, the majority of which has been to our intramural program, so $10 million intramural, $4 million extramural. And the reason really for the difference between the two is that the extramural is a newer addition to our portfolio, probably only through about the last four or five years have we funded extramural programs.

The office has funded over 150 projects

and over 100 principal investigators. And the information on this last bullet here is one of our fellows actually tried to contact all of our investigators to be able to get information on the publications that have resulted from OWH funding. And I must say, now that I better understand her methodologies, this 35 percent response rate is actually much higher than what she had. She probably had maybe about 10 percent of investigators respond to her. And of those that responded, we have research that was funded or partially funded by the Office of Women's Health actually contributed to over 120 peer review papers, and over 125 either abstracts, posters or presentations at professional meetings. So that is the 35 percent, I was actually kind of happy even with 35 percent, but what we got is really maybe 10 percent of the response, the output from what's been funded from our office is considerably more than that. And the PIs are informed that they should - they actually sign paperwork when they get funding from us that they agree to inform us of any publications or presentations, but once the funding is over, we are

off the radar screen, and it's obviously apparent then that we don't hear about what they've published.

This slide just gives you some information about the diversity of areas that have been funded from our office. You can see sex and gender differences, cancer, dietary supplements, cosmetics, osteoporosis, broad variety here. And as a matter of fact, the people in my science program are not happy with the original categorization here, and actually are going to go back and reclassify these in the near future.

So again, here's the intramural program, $10 million. This is just for FDA investigators. This is not necessarily just bench laboratory sciences, either. In 2005, the scope of our program was to fund sex and gender differences, so last year three new projects were funded. At this time, we have 25 ongoing projects that are being monitored or funded by our office, and you can see the range here. We have basic science with animal models looking at sex differences in heart tissue, drug-drug interactions for HIV therapies, and sex differences in

cardiovascular imaging.

Extramural, again $4 million, the majority of which has gone through the department's COEs, Centers of Excellence for Women's Health. And the funding from 2005, again for sex and gender, focused or actually provided funding for an ongoing study now for looking at genotypic and phenotypic differences of cytochrome P450 2B6. And then also an ongoing study which has taken several years to finish here, pharmacokinetics and pharmacodynamics of antibiotics in pregnancy, which started as an initiative from counter-terrorism several years ago, that was a result of the Anthrax episode. And the fact that there was gaps in knowledge for how you would dose certain populations. So since all I had was 2004 of sex and gender, I thought it would be helpful to show you the previous year where the scope was cardiovascular, and what was funded from our extramural program was to look at the difference in efficacy in men versus women for ACE inhibitors, safety issues for coronary stents in women, a study looking at imaging for coronary artery disease and actually the breast attenuation

that would need to be accounted for. And then the last two looking at studies in pregnancy and lactating women is to link with a critical initiative in the Center for Drugs, to move forward with a labeling regulation to change the way products are labeled in pregnancy and lactation.

And then our special funding initiative just provides us with flexibility for issues more or less as they arise. We funded several workshops through this. We funded some very quick turn-around research projects. And our science program in 2005, a little less than $1 million, and funded research in cardiovascular disease, sex differences, and specifically sex differences and cardiovascular disease where the study is intended to look at the differences between men and women.

Here is a representation of just a few of the outcomes that are of regulatory importance to the agency. And you can see from studies that were funded in our office that there has been an impact on drug development, screening products for QT prolongation, impact on drug labeling, whole cross labeling

initiative with oral contraceptives, and St. John's Wort, product quality, a study that looked at the product quality for condoms, the quality standards were changed as a result of studies funded by our office, patient safety where visualization tools looking at the adverse event reporting system was funded through our office and is a tool that is used in the Office of Drug Safety, and then a last example is a guidance document that the experience from pharmacokinetic studies in pregnancy funded by OWH, that experience was instrumental in the wording and the development of a guidance document on how to do those studies in pregnancy, where hopefully you'd end up with information on how then to dose pregnant women.

So we're hoping to build on these successes. We need to maximize our network of partners, and I see in my office a very good opportunity for lessons learned, where the outreach section can certainly provide lessons learned to our science section, and especially as the science program grows and we are able to replace the vacancies, it

would be important to utilize the knowledge that the outreach section has with establishing partnerships and leveraging that. We want to continue with investigating sex and gender differences, and promoting analysis looking at sex and gender differences. It's critical that our office translates this scientific information into language that is understandable by consumers, and we will continue to support agency and department initiatives. And to that, we have ongoing relationships with the department's Office of Women's Health through a coordinating committee. Our office is working with NIH to develop an online course on sex and gender differences, and that course will actually go live in June.

Our office, in conjunction with HRSA and NIH did an investigation of the pharmacy school curriculum specific to women's health, and we are currently now working with NIH on their SCOR's RFA, which is there specialized centers of research. This is their second go-around of the SCOR. The SCOR has a five-year grant out of the Office of Research for

women's health. It had funded 10 centers to a tune of a million dollars a year per center, so our ability to work with them with this RFA may be an optimal time to leverage what limited resources we have with the more extensive monies that they have.

So the Institute of Medicine recognized the importance of sex and gender, and actually even defined sex and gender in this 2001 publication. They also put forward recommendations for how to better understand the differences in sex and gender. In 1992, the GAO did a report on sex differences in women in clinical studies on drugs, and in 1992, they reported that women need to be included more, that there's under-representation. But in 2001, their report showed that there was sufficient representation of women in clinical studies, and actually, the problem was in the earlier studies, early Phase One, and early Phase Two-type studies, where women were under-represented.

So what we're looking for to the science board is really to assist us in expertise. Our program goes through intensive peer review, and

although FDA certainly has the regulatory expertise to review, sometimes we have a little bit of a challenge finding people who are external to the agency with appropriate expertise, so we would like to engage you in this process.

In addition, we do not have an advisory committee that counsels on what our priorities are, or helps set a priority list. And although the council that I am going to be establishing in the near future will help do that, I think that it will be very important for us to have external input, as well, as to what are high priority women's health issues that are specific to FDA products. And I think that collaborating and establishing some level of partnership will really improve our program, and I see the scientific program in OWH as something that's very exciting and has tremendous potential to grow over the next couple of years. So I leave you with FDA's mission and OWH's mission, and happy to entertain any questions.

DR. SHINE: Kathy, thank you very much. That was a very nice overview. I presume that when

you fund something internally, well maybe I shouldn't assume this - do you have to support salaries of people who are doing those projects, or is it only the content work? I'm trying to figure out how much bang you get for the buck given the limited budgets you have.

DR. UHL: There is a little bit that can go for salary support, but as more of a fellow -- Norris wants to answer this question.

DR. ALDERSON: Let me help. Typically, on the internal projects that we fund internally, there is no -- typically, no FTE support. There might be a post doc included, but we generally pay the operating cost plus, depending on the project, a post doc salary.

DR. SHINE: I mean, my reason for asking that question is that although the money is relatively small in terms of the dollar amount it in fact does give you a significant amount of leverage in terms of people who want to do things. And in that regard, what's the average size of a grant? Do you have any sense of that?

DR. UHL: Yes. We do not do grants. Our's is all by contracts, so the little subtle difference, but they're not contracts, I mean they're not grants. And they vary. Some projects have received $5,000, and some have received $200,000. To give you a ballpark, the intramural program is geared towards a two-year project to be funded at no more than $100,000 per year. But I must say, we're in the process of reviewing them now. There are several that are right there at the $200,000 mark, and there are a couple that are asking for $35,000.

DR. SHINE: And I presume in the process of awarding those, you're looking for leverage in terms of those projects which will produce the biggest influence in terms of the result, vis a vis the overall function of the organization.

DR. UHL: That's correct. It is critical that the applicant identify what the regulatory impact of their project will be. And they are free to leverage outside of the agency to include investigators from academic institutions as co-PIs.

DR. SHINE: So if you've got a project up

there on coronary stents, the project is about the regulatory process for coronary stents, or the information required to make regulatory decisions as a function of the role of women, or the design of the trials that involve trying to get approval of stents. I'm just trying to get a sense of how you connect the science to the regulatory process.

DR. UHL: You know, it could be any of those. And you've heard about the different centers today, and you've seen that some of the centers have more facilities for hands-on lab-based science, so some of the investigators are able to do their own investigations. Others look at the data that have been submitted and make analyses from that, but it's a mixture.

DR. SHINE: And in terms of your demographic studies, I presume you're also looking at the ethnicity of women in addition to their gender.

DR. UHL: WE will try. It will be challenging. It will be interesting to see what type of data we're able to get out.

DR. SHINE: Questions, comments? Dr.

Laurencin.

DR. LAURENCIN: Is there an Office of Minority Health at FDA?

DR. UHL: I do not think so, no. There's an Office of Special Health Issues.

DR. LAURENCIN: Is there a reason why there's not an Office of Minority Health?

DR. ALDERSON: I don't have an answer for that, Dr. Laurencin. Even this one was established by Congress mandate. It wasn't an FDA initiative.

DR. LAURENCIN: Fine. But I guess if it -- you could see it's important, and I think that -- I mean, because obviously, a very key question, of course, is that we know that under-represented minorities are not represented in clinical trials adequately.

DR. ALDERSON: That's right.

DR. UHL: Right.

DR. LAURENCIN: So that's one of the questions that the GAO report that came out, to answer the question, they already have the answer so we know that. And we also know there are health disparities,

so the two reasons why this office actually exists, the Office for Women exists are already plainly there, so is there a reason why there isn't? And also, there are sister organizations at NIH. It seems like in FDA, the reasoning is even more compelling in terms of having an office.

DR. SHINE: I would add to your list the whole discussion about racial differences in terms of responses to drugs, all of those kinds of issues.

DR. LAURENCIN: I brought this up before at a different meeting, but I think this even brings it out even more.

DR. SHINE: Maybe we should bring it up again with the Commissioner and see what his thoughts are.

DR. ALDERSON: Dr. Charlson just pointed out to me that at NIH there is an Office of Minority Health.

DR. LAURENCIN: Right. And an Office of Women's Health, too.

DR. ALDERSON: Right.

DR. LAURENCIN: So I'm just saying that

it's even more compelling, there are even more compelling reasons to have it at FDA, too.

DR. SHINE: Other questions or comments, suggestions for Dr. Uhl? Anybody? Has the controversy over Plan B, or RU-486, or whatever affected your credibility with women's groups, or your ability to do your work in terms of outreach and so forth?

DR. UHL: I don't think so. I don't think so at all. Obviously, any time I'm outside of the agency, I'm asked questions along those lines, but I don't think so.

DR. SHINE: And you emphasize that you don't make regulatory decisions, but presumably, you do have input with regard to, as you pointed out, health policies, so are you called upon to provide any input with regard to those kinds of issues?

DR. UHL: Well, I've been in my position for three months, and most of those issues, they're somewhat in the past, but our office serves as consultant to the divisions, to the centers, and we have ongoing relationships with the different centers.

And they bring us in on issues as they arise.

DR. SHINE: Any further questions? I think in terms of the request that you made, a number of us would be happy to help with regard to peer review of projects and so forth, if you would find that useful.

DR. UHL: That would be very helpful. Thank you.

DR. SHINE: In terms of the -- given the perhaps highly specialized nature of some of the review that's required. I don't think that would be a burden. I wouldn't like to see a whole bunch of $5,000 projects, but certainly in terms of key issues, I think we'd be happy to try to help in an informal way. I'm impressed that with a relatively small budget, you seem to be having a significant impact, and we certainly hope that you'll continue to do that, and we wish you every success, particularly in view of the fact that you've only been doing this job for three months. We'll have to look more closely at how and in what way we can play a role with regard to the portfolio, which is a somewhat more focused kind of

activity, and we'll discuss that.

DR. UHL: Thank you.

DR. SHINE: Thank you. Ladies and gentlemen, we are proceeding at a remarkable pace. Let me just make a few overall comments, because I don't want to keep anyone over-long. I think we received an excellent charge from the Commissioner this morning with regard to an important new role for this board. I've asked Gail Cassell and Allen Roses, Cato Laurencin, Susan Harlander and Barbara McNeil to become a small working group, and it is our intent to have some telephone conversations, and probably at least one in-person meeting face-to-face in the next couple of months to try to develop a template for how and in what way we would proceed to respond to the Commissioner's charge.

We also feel that if we can, indeed, develop that kind of approach, that we might do some pilot activity, but I would emphasize that our activities in this regard are entirely data collection in preparation for another meeting. We will make no decisions, we'll take no votes, and we will not

otherwise give Jan a hard time. We do have a sense of urgency, and I've asked Gail Cassell to chair the working group because she wants it done tomorrow, and I think that's a promising kind of experience.

I appreciated the update on drug safety. I think the board continues to see this as an extremely important area going forward. While we're not going to ask for updates at all of our meetings, you can be assured we will continue to ask questions about the progress being made. I certainly was pleased with the presentations today with regard to, in comparison to our original meeting, on this subject that growing the database in terms of patients covered. I'm not sure it's tens of millions that Steve was talking about, but it's certainly over 10 million in the initial pool, but hopefully that will expand. I think we do need a 20 or 30 million person pool if we're going to have a high level of confidence that we are addressing or discovering adverse events. And I would encourage the agency to continue to push hard. Unfortunately, I've had personal experiences too often with Vicilin-CR and Vicilin-LA, and the same container looking

exactly the same at one time, except for LA and CR. And we've just -- I think the agency can make a major contribution by making sure that we don't have too many more cephalo-this, or cephalo-that, and making sure that the packaging and the appearance is distinct.

I would congratulate the agency on the new physician labeling insert. I think it is much more legible, much more readable, much more understandable, and I think that in the roll-out of that, I received a number of inquiries and telephone calls about why was this being done, and what did it mean, and all the rest of it. Well, I think it was based on focus groups which told us what physicians needed to and wanted to know, and while there are still concerns about how far you have to read down to get to every last complication, the fact is that in a risk assessment environment, knowing what the major risks are, knowing them quickly and in a form that is accessible to the physician is really important, I would like to encourage the agency to move forward with similar kinds of focus groups with patients in

terms of the patient materials, given among other things the reading level of our population these days, and the necessity that patients get that same kind of drug insert information in a form that's readily accessible to them.

I'm very pleased with the response from ORA. I think, Kathy, that it was a prototype of a very nice review process. We'll try to build on that with the NARMS review, and it's my hope that we can continue to do those and similar kinds of inquiries in parallel with our overall look at the science portfolio.

I will be talking to a couple of people more about joining the review of NARMS, and I'll work with the staff with regard to putting together the final review committee. We're not looking at a huge number of people. We think that if we select people carefully, five or six people ought to be able to conduct the review. I think if you have really good scientists doing what needs to be done, you don't have to have necessarily a world expert on every single part of what it is you're looking at. But what you do

need is people with good scientific taste, and understanding how the program goes.

I was pleased that we were able to get an overview of the Women's Health program, and I think we should communicate Dr. Laurencin's concern, as well. I am interested, Cato, in Dr. Uhl's concern that she may not be able to get the ethnicity of women as much as I would like to see. It seems to me that if we're going to look at the issue of gender, we ought to be looking at racial differences and so forth as part of that, but then the whole issue of minority populations in terms of what goes on, as a cardiologist, I'm struck as I did clinical trials on nitroglycerine and hydralozine 20-odd years ago, and you know the story of what's happened with that in terms of the racial differences and response, the alleged racial differences, the apparent racial differences that have occurred with that combination.

Are there any other comments that any members of the science board wish to make? Jan, Norris? Thank you very much. I appreciate your input and we'll move forward. We are adjourned.

(Whereupon, the proceedings went off the record at 2:51:12 p.m.)