U.S. FOOD AND DRUG ADMINISTRATION

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SCIENCE BOARD ADVISORY COMMITTEE

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MEETING

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FRIDAY,
NOVEMBER 4, 2005

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The meeting convened at 8:30 a.m. in the Versailles Room of the Holiday Inn Select Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, Kenneth I. Shine, M.D., Chair, presiding.

PRESENT:

KENNETH I. SHINE, M.D., Chair
GAIL H. CASSELL, Ph.D., Member
JOSEPHINE GRIMA, Ph.D., Member
SUSAN KAY HARLANDER, Ph.D., Member
CATO T. LAURENCIN, M.D., Ph.D., Member
BARBARA J. McNEIL, M.D., Ph.D., Member
F. XAVIER PI-SUNYER, M.D., M.P.H., Member
JIM E. RIVIERE, D.V.M., Ph.D., Member
ALLEN D. ROSES, M.D., Member
KATHERINE M.J. SWANSON, Ph.D., Member
JOHN A. THOMAS, Ph.D., Member
JAN N. JOHANNESSEN, Ph.D., Executive Secretary

FDA STAFF PRESENT:

NORRIS E. ALDERSON, Ph.D., Associate Commissioner for Science
ROBERT E. BRACKETT, Ph.D., Director, CFSAN
M. MILES BRAUN, M.D., M.P.H., CBER
ANDREW VON ESCHENBACH, M.D., Acting Commissioner of Food and Drugs
STEVEN GALSON, M.D., M.P.H., Director, CDER
LARRY KESSLER, Sc.D., Director, Office of Science and Engineering Laboratories
JOHN R. MARZILLI, Deputy Associate Commissioner for Regulatory Affairs
DANIEL SCHULTZ, M.D., Director, CDRH
WILLIAM SLIKKER, JR., Ph.D., Deputy Director for Research, NCTR
STEPHEN SUNDLOF, D.V.M., Ph.D., Director, Center for Veterinary Medicine
DOUGLAS C. THROCKMORTON, M.D., Deputy Director, CDER
JANET WOODCOCK, M.D., Deputy Commissioner for Operations
LINDA YOUNGMAN, Ph.D., Center for Veterinary Medicine

PUBLIC HEARING PARTICIPANTS:

SADHANA DHRUVAKUMAR, Senior Scientific Research Specialist, PETA
SUSAN PROLMAN, Union of Concerned Scientists

I-N-D-E-X

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

8:30 a.m.

CHAIR SHINE: Good morning, ladies and gentlemen. We're pleased to welcome you to the fall meeting of the Science Board Advisory Committee for the FDA. I'm Ken Shine. I currently serve as chair of the committee. We're very pleased that Acting Commissioner von Eschenbach was able to join us. In a few minutes we'll ask him to make some comments. However, I thought since this is his first meeting with this group that it would be useful if we just ask the members of the committee to identify themselves and say a sentence or two about your area of interest or background so that he could begin to put names with faces and so forth to the extent it's possible. We also want to recognize two members of the committee who are graduating. We'll do that immediately after we do the introductions. So if we could start I guess?

DR. RIVIERE: Hi, Jim Riviere. I'm the Distinguished Professor of Pharmacology at North Carolina State University in veterinary medicine and toxicology.

DR. GRIMA: I'm Josephine Grima. I'm the Director of Research for the National Marfan

Foundation, and I am a member of the National Organization for Rare Diseases.

DR. THOMAS: John Thomas, Professor of Pharmacology and Toxicology, University of Texas, Emeritus.

CHAIR SHINE: Now at Indiana.

DR. SWANSON: I'm Katie Swanson. I'm Vice President of Food Safety with Ecolab, and I focus on obviously food safety and food microbiology.

DR. PI-SUNYER: I'm Xavier Pi-Sunyer, Professor of Medicine at Columbia University, head of the Division of Endocrinology at St. Luke's Roosevelt Hospital, and my interest is in obesity, diabetes, and metabolic disease.

DR. LAURENCIN: I'm Cato Laurencin. I'm the Pratt Distinguished Professor of Orthopaedic Surgery at the University of Virginia. Also Professor of Chemical Engineering and Biomedical Engineering.

DR. HARLANDER: My name is Susan Harlander. I come out of the food industry and academia in the area of food science. My specialties are genetically modified foods and food bioterrorism.

DR. CASSELL: I'm Gail Cassell. I'm Vice President for Scientific Affairs at Eli Lilly, and my area of interest and expertise is in infectious

diseases.

DR. ROSES: I'm Allen Roses. I'm Senior Vice President of GlaxoSmithKline. My area of interest is in pharmacogenomics and molecular directions for therapies.

DR. MCNEIL: I'm Barbara McNeil. I'm head of the Department of Health Care Policy at Harvard Medical School, and I'm a radiologist at the Brigham and Women's Hospital in Boston.

CHAIR SHINE: Dr. McNeil has just joined the committee. She's a new member. We have -- the first two people who introduced themselves are actually completing their terms, and we want to acknowledge their contributions. You already heard from Dr. Josephine Grima that she's Director of Research and Legislative Affairs for the National Marfan Foundation. She administers a substantial grant program there. She does outreach, including to the NIH and other advocacy organizations, and she has a background in science, having received a Ph.D. in molecular biology, and, as you've heard, is a board member of the National Organization for Rare Diseases. She's provided an important perspective to this committee from the point of view of patients and the concerns that they have about the activities of FDA.

We want to thank her for her services, and I'll ask Dr. von Eschenbach if he would present her with this plaque commemorating her service.

As you heard, Jim Riviere is the Burroughs Wellcome Fund Distinguished Professor of Pharmacology. He told you he was a Professor of Pharmacology, but he's actually the Burroughs Wellcome Fund Professor, and Director of the Center for Chemical Toxicology Research and Pharmacokinetics. He's a director of the biomathematics program at the School of Physical and Mathematical Sciences at N.C. State. He has many, many, many awards, medals, recognitions. He's edited some 10 books in pharmacokinetics, toxicology, and food safety, and he's been a very important member of the committee, particularly in areas related to pharmacokinetics toxicology, and we're very grateful for his service.

Again, thank you both for your help, and we look forward to your wise advice in the future as well. We now have to have Jan Johannessen read the proverbial words of wisdom. Jan?

DR. JOHANNESSEN: Thank you. The following announcement addresses the issue of conflict of interest with respect to this meeting. It 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, Riviere, Grima, Laurencin, Swanson, Thomas, Roses, Pi-Sunyer, Cassell, Harlander and McNeil. A copy of the waiver statements may be obtained by submitting a written request to the Freedom of Information Office. Waivers permit them to participate in the committee's discussion of the FDA's drug safety programs, BIMO Initiative, and Science Board peer review activities on the agenda for today.

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 practical to recite all potential conflicts of interest as they apply to each participant. The FDA acknowledges 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 open public hearings scheduled for

12:30 today. I would just remind everyone to turn their microphones on when you speak so that the transcriber can capture all the comments. Thank you.

CHAIR SHINE: Thank you very much. And if I can keep this on. My current responsibility is as Executive Vice Chancellor for Health Affairs in the University of Texas system. In that capacity I'm responsible for a number of health institutions, including the MD Anderson Hospital. We're very pleased today to have with us a commissioner who spent much of his professional career at that institution. It was well known that if you had a urologic problem related to cancer, that Andy von Eschenbach was available to help. He had a very distinguished career as an academic urologist. He had important responsibilities at MD Anderson for the oversight of the academic program. And therefore, it was not a complete surprise when he moved to Washington to become the Director of the National Cancer Institute. As I suggested, he's there to help. Little did he know that five weeks ago, when the responsibilities of the Commissioner of the FDA suddenly had to be dealt with, that Andy was prepared to help. And five weeks ago, give or take a day, he became the Acting Commissioner of the FDA. I still haven't figured out

exactly how he's managing to relate to both the National Cancer Institute and the FDA, but he's been trying hard to sort that out. We're very pleased that he's able to join us this morning and bring the kind of expertise that he had in clinical practice, that he's had in research in terms of what's happened at the NCI, and his interest in the delivering of products for patients which are safe and effective to the current position that he holds. Welcome, Commissioner, and we are pleased to hear from you.

DR. VON ESCHENBACH: Thank you very much, Ken. I must admit, ladies and gentlemen, it's kind of nice and fun to be able to get such a warm welcome from a fellow Texan, even though neither he nor I sound that way. I want to begin by first of all apologizing for the fact that I will not be able to be with you for the entire day. And that is not because, obviously, of the fact that the work that you're doing is not of critical importance to me and to the FDA, but rather one of those issues of a prior commitment that I must meet, and so therefore I hope you'll forgive me this time. But I want to assure you that in spite of the fact that I cannot be with you all day today, this board and your effort is in fact one of the areas of highest importance to me, and one which I

am very enthusiastically looking forward to bringing a great deal of my own personal commitment and investment and involvement.

I thought this morning I would like to begin by first of all, in light of how important the work is, to begin by thanking you. And thanking you for the tremendous effort, the amount of energy, and I'm aware of the amount of passion that you bring to the effort in support of and helping the FDA as it goes about its critical important work across what is an unbelievably diverse portfolio of responsibility. And I hope that you will always know how grateful the FDA itself is and the people who make it up, and how grateful its commissioner is for that effort.

I wanted this morning in the time that we have available to just use this as the beginning of what I would like to be an ongoing conversation, an ongoing dialogue between you and me as the commissioner for as long as I am privileged to be in this role. And in the context of this being just the beginning of that dialogue, there's so much that I would like to share with you, and will look forward to sharing with you, but with the time that we have available I'll only be able to deal with a portion of the many things that I'm looking forward to

discussing, sharing, and asking your wisdom and your input about. The things I thought I'd like to use my time this morning for was to, one, just introduce myself to you, and to share with you a little bit about who I am and what I think and why I do the things that I believe are so critically important, because I think it is important for you to know me and to understand me. I also then would like to spend a few minutes talking a little bit about the relationship that I would look forward to between the FDA and myself in the role of commissioner and with the board, and how that might in fact look as we go forward on this journey together. And then, the third and final thing that I would like to share with you is a brief perspective of a vision that I personally have, and that I think is relevant to the FDA, and where I believe we have enormous opportunity to begin to further create the FDA of the 21st century, building on the unbelievable record of accomplishment and achievement that the FDA has accomplished over the past hundred years of its existence.

With regard to my own personal, I really come to this opportunity with a strong belief that regardless of what our roles and responsibilities are, there is only one common purpose that binds us

together, and that is the health and welfare of the people that we serve, not only the people of this nation, but because we are the United States of America, the people of the world. And I view that the FDA, as I did at the NIH and the NCI, that the critically important work that we do is not the end in itself, but it is a means to an end, and that the end is that person's welfare and health, that individual that we serve, whether it's a cancer patient, or whether it's the public looking forward to being able to continue to not fear the food that they eat or worry about the safety and the efficacy of the medication they give their sick child before they go to bed. And so I will continuously work to focus the efforts of the FDA and my own efforts on the purpose and the reason why we're here in the first place. In that regard, I am therefore strongly aware that if we're going to best achieve the end that we set out, regardless of how powerful, regardless of how talented, regardless of how extensive any one agency or organization is, none of us can do it alone. So a hallmark that you will see me constantly addressing and expressing is the hallmark of collaboration, cooperation, integration, finding a way that we can continue to excel as individuals, be it an individual

investigator or an individual organization or institution, find ways to collaborate and to cooperate.

In that regard, one of the wonderful experiences that I had that I think has been an important part of my excitement and enthusiasm for being in this role now is when I was at the NCI and when I came four years ago to the NCI, recognizing that the critically important work of the NCI to eliminate the suffering due to cancer could not come about without collaboration and cooperation with the FDA, and the important work that it was doing. So I had the good fortune, as I was sharing with some of you privately, when Mark McClellan was confirmed as commissioner on a Thursday night, to have our first one-hour meeting the next morning at 9:00 a.m. in his office, where we put the NCI/FDA Joint Task Force together. And that gave me an opportunity at very close hand to become even more aware of the critical, important work of the FDA. So I want to share with you the fact that I come to this role with a great deal of respect and a great deal of appreciation for what the accomplishments and achievements are, and what, in fact, the efforts are of the many talented people who are sitting around this table and in the

audience who make up the FDA and are responsible for its greatness. And so with that respect for the work of the FDA, I come to this role not to be a simple caretaker, not to simply be in an acting role such that there is a suit sitting at the head of the table, but I come to this role to be fully, completely immersed and engaged in supporting and nurturing the important work of the FDA. It is too critical and too essential to everything else for it to falter or to in some way be impaired or impeded. And so for as long as I'm here, what I would like you to know about me is that I'm going to give this effort my full energy, full attention, and I am going to do that in a context of serving and assisting this agency to continue to move forward as aggressively as it needs to to meet its responsibilities and the expectations of those people, patients and the public, that we serve. And so I think as many of the people at FDA have already become aware, I am action-oriented. I am very much looking forward to working with them, to be very aggressive about our role and responsibility and the need to move forward. And I want the board to be assured that for whatever period of time I am here, that they need not be concerned that we will be in a holding pattern, but rather will continue to drive the

very important work that you have been advising and helping the FDA to formulate as its agenda. And I will do that in the context of attempting in every way possible to provide the leadership to the FDA that drives that coordination, that integration, both within the agency itself so that we synergize and maximize our own effort by greater internal collaboration and cooperation, but also to serve to even more effectively integrate the FDA in many of the activities that are occurring outside, whether it's in other federal agencies, or in the academic community, or in the private sector. And probably there's no more important area for that to be expressed in right now than our recent, very recent, within the past week, important emerging role in the whole area of pandemic flu. And so with that in mind with regard to the commitment and the perspective that I would like to bring to this role, I also believe that it's critically important if we're going to move aggressively in those directions that we benefit and profit from the wisdom of others who have perspective that goes beyond our own. And that brings into play the critically important role of a board such as this. I look forward to a close working relationship with this board on an ongoing basis, not just at the times

we have meetings but even in the interim, through the appropriate mechanisms that will allow you to provide meaningful and significant input into the many issues, many areas of emphasis among the important plans and programs that we are embarking upon or considering at the FDA.

I do not believe that boards should be created simply to provide an organizational structure pro forma chart that appears that the agency is functioning in some way with oversight. I believe that boards, especially one like this in which you are asking very gifted, very talented, very committed individuals to give of their time, their energy, and their effort, that what we then owe you in return and in respect for that effort is that it be meaningful, and that we will work together to be sure that that time that you spend and energy, that passion that you bring to the FDA is in fact a precious resource that we will appropriately utilize.

We will work together to define exactly how that will evolve and play out. There are many important areas and initiatives that I would look forward to exploring with you and benefitting from your input and your advice. And that perhaps leads me to the other item that I wanted to share with you this

morning, and that is a view or a philosophy that I would share regarding the future. I believe very strongly that we are in the midst of not what is really a revolution, but perhaps even better described as a metamorphosis. That for thousands of years we have had to view diseases, and I'll speak in this regard more personally from the perspective of my experience in cancer, but we have been faced with viewing a disease like cancer based on what we could feel, or what we could see. And perhaps a hundred years or so ago we had the benefit of going from that macroscopic perspective to a microscopic view of disease. And although that changed things, and although that macroscopic and microscopic view may sound like ancient history, in fact, as Ken pointed out, when I went to MD Anderson in the `70s and even into the `80s, although that macroscopic and microscopic view of thousands and hundreds of years seems like ancient history, the reality was even just a few decades ago that the only way I had of detecting the most common cancer that occurs in humans was what I could feel with the tip of my index finger. But maybe ten years or so ago we moved from that macroscopic and that microscopic view to a molecular view. And that new reality of a molecular perspective

has not changed one thing; it's changed everything. It is not a transformation, but really, in my opinion, is a metamorphosis, such that the future, the future that the FDA will be a part of creating and being responsible for, is no more like the past than a butterfly is like a caterpillar. The future that we will be able to create across the entire diverse spectrum of the FDA, whether it's in fact related to issues having to do with veterinary sciences, or issues having to do with food and nutrition, or drugs, biologics and devices, and on and on, all of that portfolio in the future that we will be creating will be influenced and determined by a molecular perspective and a molecular vista. This then places an extremely important part of our emphasis on the idea that FDA must not just be a science-based regulatory agency, but in fact a science-led regulatory agency. In exploring and determining the opportunities that science will provide for us in helping the FDA to position and determine and posture its efforts and its activities to not just be a part of, but in many ways lead and be responsible for that new future, is going to be a critically important area for discussion, thought and deliberation.

We are seeing on the science end of the

perspective from the discovery point of view enormous progress that's almost occurring at an exponential rate in terms of our beginning to unravel the fundamental mechanisms and bases for diseases like cancer and others. The genes, the molecules, all of those parts and pieces are better known to you in your own field of expertise than perhaps even to me. But that discovery must be rapidly translated into development of interventions that are then able to be delivered in a way that alters and changes the reality, the reality across the entire spectrum for those patients and that public that we serve in the first place.

I will look forward to my time at the FDA being a part of helping to be thoughtful and deliberative about that future, about the future that the FDA will be creating and responsible for. There are lots of details that need that broad philosophical overview, details that I look forward to continuing to evolve and develop with the very important talented leadership within the agency across its centers and across its offices, but also with you, and the perspectives that you can bring to these very important deliberations and conversations as we go about the important work that you have been a part of

and that they are responsible for. It for me has been an incredible privilege to have been asked to serve in this very, very important way. All of us recognize that the circumstances under which that occurred were difficult. They were difficult for everyone involved, and especially difficult for the FDA and the people who make up this wonderful agency. I believe that in spite of how this came about, the fact of the matter is that there is great opportunity within our grasp, and I'm committed and very intent and dedicated to making sure that that opportunity does not in some way slip from our grasp. And I will pledge to you to work collectively with you to define the ways and opportunities that you can help ensure that opportunity is realized. It literally has millions of lives depending upon it. So thank you, Mr. Chairman, for the opportunity.

CHAIR SHINE: Thank you very much Commissioner. Questions, comments from the board? Dr. Cassell.

DR. CASSELL: At a time when in fact -- first of all, I really very much appreciate what you've said and resonate with it tremendously. It seems to me that in order to be able to accomplish your vision that will require considerably increased

resources for FDA, and this is something that troubles me a lot because, unlike a lot of our other favorite agencies, FDA doesn't have the advocacy groups much like NIH has, for example, in terms of funding, or CDC, and I wondered what your thoughts are about being able to accomplish this, particularly in a time when the budget is so constrained. And I look at the food plan, for example, that was released on Wednesday by President Bush, an increase of almost $8 billion, and yet there were no dollars for FDA. But if you look at the needs in terms of new antivirals and also new vaccines and vaccine manufacturing, it seems to me a large part of what needs to be accomplished will have to be done, you know, by direction and leadership through FDA, but yet no additional resources. And what are your thoughts about that? Maybe you can't say too much about it, but these are the things that are worrying me right now.

DR. VON ESCHENBACH: Well, they're extremely important issues because one of the obvious observations is when you look at the FDA and its scale and scope of responsibilities, and then the resources that are required to meet those responsibilities, it's an agency that is working at its limits and at its maximum. The people within the agency are working

extraordinarily hard to be able to continue to meet the expectations and the needs, and as those opportunities and needs increase, we're going to have to find ways to be strategic in how we will continue to increase the resources available.

There are multiple layers to that that we're already beginning to engage in. One is for me to look internally within the agency to find where there may be opportunities for greater synergy, greater interaction among parts and components of the agency, to use more efficiencies in terms of what can be accomplished. That may not have a large opportunity for yield because we may very much already be close to those limits, but I'm going to drive and look anyway as hard and as carefully as we possibly can.

Second is to look where there may be opportunities for leveraging the resources for greater opportunities for collaboration in which we may be able to accomplish mission, accomplish goals, by finding ways to partner. And I think in that regard one of the first places that I believe is a great opportunity for us is to explore even further collaborations with NIH in which we may be able to integrate and wed programs together in ways that can

meet some of those responsibilities.

And third, you are absolutely correct in two areas. One is our internal communications and the other is our external communications. I believe we need to make the case statement more effectively, more effectively with our constituents, the public, and there are real opportunities and challenges with regard to communication. In many ways FDA's great work is known primarily only to those who are closest to it, and it is just taken for granted by everyone else. I think we need to help others who take it for granted that we can go to bed every night putting our head on our pillow and not worrying about the food we ate, or the food we gave to our pets, or the medicine we gave to our child without even wondering how that came about. I think we have to be more effective in helping people understand what the return on their investment is yielding, and why that investment is so critically important and perhaps needs to be even further enhanced and grown, especially during a time when the challenges to that comfort level are increasing, whether it's through food importation, or whatever other issues, the expanding portfolio of new drugs and devices, et cetera. So the challenge is there. And with regard to internal communications,

much more effective wedding of a business plan to our strategic plan that enables us to in the beginning of the process be more effective at being able to represent the critically important components that FDA must contribute to an initiative like pandemic flu, and a very realistic, well-developed, rigorous business plan that justifies the resources that are required for that contribution to be made. And that's a discipline and a rigor that is difficult but critically essential when we are competing for very, very precious resources.

CHAIR SHINE: Any other comments or questions? I would just say, Gail, that the Commissioner has indicated that he does want input from the board on its own agenda. And I would argue that telling the story of the FDA in '06 for historical reasons may be a very high priority. I think the board also should raise the question of as the program dealing with pandemic flu evolves, should we examine that from a scientific point of view, and is that an area where we want to be more explicit about what some of the needs are and so forth. So I think there are a variety of strategies that we'll want to work with the Commissioner on in terms of how and in what way we follow up with what is a critically

important issue that you point out. Commissioner, we're very grateful for you're being here, even if it's only part of the day. Given the history of your responsibility, you're properly excused whenever you want to go, and we're going to go on with our session, but we look forward to working with you on identifying the strategic areas where we can try to provide some help.

DR. VON ESCHENBACH: Thank you, Mr. Chairman. The one very strong comfort level I have in taking my leave is that I can stop looking to my left but look to my right and know that I'm leaving the board in fabulous and fantastic hands. And so I am confident, not particularly comfortable in leaving with you, but I am confident in leaving you that I've left with you the best of FDA. But I will look forward to being with you on a more extensive basis as we go forward.

CHAIR SHINE: We'll move forward to our program. Jan has another announcement. Jan?

DR. JOHANNESSEN: Excuse me. The hotel has asked is there an Eric Phillips in the room? No, okay.

CHAIR SHINE: He didn't pay his bill, is that? Oh okay, it's a parking problem. The board has

had a continuing interest in drug safety, and we're very pleased that Steve Galson, the Director of the Center for Drug Evaluation and Research is going to give us an update on drug safety issues. Steve?

DR. GALSON: Okay. I'm going to zip through my slides, and Jan, if you could help me stay on track since I'll be looking this way. And sorry, I hope you all have flexible necks so you can look at me and look at the board at the same time. Next slide.

You may recall from last spring we gave you quite a tutorial on drug safety, and I'm going to quickly go through some of the highlights of that, talk about it a little bit more, update you on some of what's happened since we talked to you last on some of the external studies and investigations going on in the agency on drug safety, talk to you about our progress on internal policy changes, what's happening with our drug watch guidance which we told you about, what we've been doing since we saw you last on our evolving expert peer reviewers and the public in giving us input and advice on moving forward in drug safety, a little bit on budget personnel organization, and then I'm going to turn it over to my Deputy Director Doug Throckmorton, who's going to talk to you in more detail about what's been happening with our

new Drug Safety Oversight Board. And then we'll have some time for questions. Next slide please.

This is what we all told you about for a good half of the day or more last spring. So at least those of you who were there are experts in drug safety and in what we do, and I know you remember every single word of it. Of course I'm not going to review it, but I did want to point a few key -- next slide -- a few key points from the spring meeting. The first is that despite what is out there in a lot of press and other reports, drug safety is a key top priority for the Center for Drug Evaluation and Research across the board in the center. We spend a full 50 percent of our resources on drug safety. It plays into the work of every single office, from compliance to new drugs to our communications work to of course the Office of Drug Safety. It's spread throughout, and it's a key priority. As you heard last spring, there are a huge number of new initiatives under way to approve both pre- and post-market analysis of drug safety information in our decision-making, and new ways of communicating with the public early about drug safety and risks.

The third major point I wanted to highlight is much of what Dr. Woodcock talked about

last spring, and that is the point that really fundamental important progress in drug safety can only really be made and is going to be made with continued scientific investments and scientific progress. And I just want to illustrate that with the next slide. This is just one of Janet's slides from last spring. It talks about and really ties in beautifully to what Andy was just talking about with the molecular metamorphosis, and that is the increasing use of genetic, genomic, proteomic and metabolomic markers in both drug development and drug safety. The idea here is that we can look at the status of patients with serious side effects versus those without with regard to these markers. These sort of connections could be used both in prospective trials and looking at our reports in our MedWatch system of adverse events that come in to try to look for the presence of these markers. By doing the science in a forward-seeking way, we will over years develop the ability to avoid high-risk patients, those patients who are going to develop adverse events that are serious from the use of the products that are on the market, and also give us better ability to monitor for development of those side effects before overt toxicity occurs. We have this capacity in a very, very small percentage of new

drugs that have intense genetic work done before, in the cancer area in particular, but there's a huge amount more that needs to be done. Much of this work is under way. Much of it is tied into the goals of the Critical Path Initiative that you've heard about before. And this is really the way that we're going to make fundamental change in drug safety in the United States and around the world. Some would argue that much of what we're doing now, and much of what I'm going to talk about for the rest of my time here is really nibbling around the edges compared to the real fundamental change we can make in scientific improvements. So, next slide here.

We're continuing to work very closely with the Institute of Medicine on their large drug safety study, and I talked recently to the Executive Officer of IOM and she told me that she really sees this as one of the most important studies that IOM has ever done. We've had a large number of both face-to-face meetings with the board, and larger exchanges of information. They seem to be intensely interested and engaged right in the middle of their information-gathering, and I'm very, very -- feeling very positive about their ability because of the strength in the members of that board, and how much they're engaged to

really give us very, very useful recommendations at the end.

There's also a large General Accounting Office study of drug safety that's under way. They've done a lot of interviews. Of course, they don't have the same sort of capacity to apply real technical and scientific expertise to the task that IOM does, so I expect a somewhat different tenor and type of recommendations from them. As well there are a number of open congressional investigations that are of a different sort, of course, completely on specific drug safety issues. A number of those are still open, and we may or may not get recommendations out of them. Some of them have resulted in proposals for legislation, and of course it's unclear where those proposals are all going. Next slide.

We also have progress underway internally with policy development and changes in policy within the Center for Drugs, and this ties in to what we said last spring and what I'll emphasize at the end of this talk, which is that while we wait for recommendations to come out of these large investigations and studies, we're continuing to make changes as we see fit. We think that's our responsibility and we need to do that. So we're working very intently on improving our

standard operating procedures on how our different offices, particularly our drug safety and our new drugs office, work together on safety issues and on other areas of communication and making decisions together.

We're also working on implementing quality systems across the agency. I think you're familiar with this from previous talks. It's basically systems that allow us to continually evaluate the quality of what we're doing, and make changes to improve the quality where we detect things that aren't working as well as they can. And there are lots of teams working on specific process improvements in the way both the Office of New Drugs and the Office of Drug Safety operate. Our managers are very, very engaged, and this is moving forward over the next year or so.

We're also working to really change the way that we communicate with the public about drug safety issues as they emerge, and Dr. Throckmorton is going to talk a little bit about this with regard to the drug safety board, the health care provider and patient sheets that we're posting on the internet and making available so that people don't have to wade through dozens of pages of the drug's official label to get key information about safety. Then we're also

working on putting together a concept to publish a new adverse event newsletter, which reports to the public about actual reports that are coming into the AERS system. This is the Adverse Event Reporting System. These reports, once we receive them, are considered public information anyway, and we want to make sure that as soon as they come in, if they're relevant and can be used by the public, we make people aware of them, even if they haven't been fully vetted, analyzed, and full implications aren't understood, very similar to some of the case reporting that goes on in the MMWR about infectious diseases that the CDC does. Next slide.

The proposed Drug Watch draft guidance. This is a draft guidance that we put out, we told you about before, that will create a list of drugs posted on the internet that we are actively investigating that we propose calling the Drug Watch. There was an open public comment period on that guidance. We got many comments. We're right now collating them, putting together, trying to look at common themes. There is support in those comments for us doing the kind of early communication that we are doing, but there are also a lot of unfavorable comments about the Drug Watch itself, the way that it's described in the

guidance that people think, some people think actually that we could cause harm by preventing patients from wanting to use drugs that may be listed on that watch. So this is always the risk/benefit balance that exists with putting information out to the public about drugs, and we're going to have to sort our way through that in finalizing this guidance. Next.

We've also continued to seek public comment, as we said we would, and our normal expert peer review system that is underway in the center has been really ramped up in the last year or so to get more of these activities going. We've had what are called under our regs Part 15 hearings. These are basically listening sessions where we get together and invite outside experts in specific fields to come in and tell us what they think about what we're doing and improvements for change. And they frequently predate guidance changes or rule changes that we may propose. We just had one this week on direct consumer advertising, a very important way that patients and physicians get information, and we're planning one for December about risks, specifically risk communication efforts that the agency does.

There's also a survey underway, physicians' preferences on risk communication, asking

physicians how they prefer to get the information. We all know that this is a changing environment because of the predominance of the internet and other ways that physicians get information that they didn't used to.

We've also had a large number of our typical advisory committee meetings. Many people don't recognize that we have, every one or two weeks in CDER, an advisory committee meeting on one issue or another, and these are really the bread and butter way that we get outside information, and a lot of that has had to do with drug safety over the last six months or so. In specific we had a meeting of our Drug Safety & Risk Management Advisory Committee in May that looked at how we do risk assessment for marketed drugs, and got some very, very useful recommendations from the committee. I would say that many of their recommendations would require substantial investment of funds on the part of the agency to implement beefed up systems of surveillance and communication, and some of them we'll be able to act on, and others are going to have to depend on getting partners and getting more support as you heard from Dr. von Eschenbach. Next.

Very quickly, just to go through, we've got a couple slides of the advisory committee meetings

that have been held since we saw you last. Many of these were key drug -- they focused mainly on drug safety issues. I'll just point to a couple of them. The question about switching to over-the-counter status for some corticosteroid products. And these over-the-counter switches really hinge on whether the drug can safely be used without the intervention of a physician. There also was a recent meeting on the benefits and risks of antibacterial soaps. Next. That we probably all have in our homes. I'll just point on this one in particular to the second from the bottom, the psychopharmacologic advisory committee that dealt with a very, very contentious issue that's been in the news a lot of how to gather better data on safety and efficacy of the use of antipsychotic drugs, and whether we should be requiring longer term studies before we approve these products, a very, very contentious issue that I don't have the time to go into here. Next slide.

In the drug safety budget, people organizational side, really, really good news. And this is when I've received sympathy from my family, and friends, and colleagues over the last year about all the controversies about drug safety. They frequently say there's a silver lining in this, you're

probably going to end up getting more money. And I'm happy to report that as we near the end of the FY 2006 budget cycle, even though we've already started the year as you know, Congress is still working on it. It looks like we'll have about a $10 million increase for drug safety activities in CDER. And that's, you know, that's a significant amount of money. It's not really what we need, but it will enable us to move forward on some of the recommendations and initiatives that we have going. So that, again, is good news.

We have hired a new director of the Office of Drug Safety, Gerald Dal Pan, after a long and very, very difficult search. He is currently a division director in the Office of Drug Safety, in the part that does some of the research and surveillance activities. He's very, very highly qualified, highly respected around the agency and outside he's just been getting started. And we're very excited and grateful that that process is over. We talked to you about that last spring as well.

We also announced in the last few weeks a reorganization plan for the center. And the major goal of that having to do with -- I want to touch on the drug safety sides of the reorganization that I announced, and that was that the placement of the

organization has to really reflect the level of commitment to drug safety. And we emphasized this repeatedly with you. We need focus and consistency in how we communicate about drug risks and benefits. We really needed a focus for cross-center policy development, which we didn't really have in the organization that we've got right now. With regard to Critical Path, in particular the drug safety parts of that, we wanted to emphasize that in our organizational structure as well, and really provide a locus for those activities in the center. Next.

So we're announcing a creation of a new Associate Center Director who will focus on development of drug safety policy, and how to improve how we communicate about risk. We're going to consolidate some key risk communication activities that exist now in different places around the center, and we're elevating the organizational status of what is currently the Office of Drug Safety to report directly to the Center Director. So this gives it the same level in the organization of some of our other senior managers, particularly the Office of New Drugs.

We're also creating what we call a new super office combining our clinical pharmacology activities, our biostatistics activities, and the

Critical Path projects that I mentioned, including other cross-cutting science activities, to report directly to me as well. And again, this is going to create a new focus for some of the activities we've been talking to you about over the last year.

So that's a quick tour de force of what we've been doing since we talked to you last on drug safety. Next. We're going to, just to summarize, continue a high level of focus on improving what we do, both with analysis of drug safety information before approval, after approval, and communicating about that to the public while we continue to work with these outside groups on their studies, and look forward to their recommendations. So next.

I want to turn it over to Doug, who's going to talk specifically about the drug safety oversight board and what they've been doing, because I know you all were specifically interested in that. We look forward to getting your comments. Thanks.

DR. THROCKMORTON: Thank you very much Steve, and thank you Mr. Chairman, ladies and gentlemen. Thanks for the opportunity to come back before you this morning. I will be talking about a new organization within CDER that has been created as a part of addressing the drug safety issues that have

come up. In the last meeting I think you very presciently suggested that this particular board, with its mix of people from within CDER, and people from within other parts of FDA, and people outside of the agency altogether, the Veterans Administration, etcetera, was really quite new to CDER, and was something that you really wanted to hear how it was going as it unfolded. And that's what I'd like to talk about today. So next slide, please.

What I'd like to do is just briefly remind you of the structure of that organization, the Drug Safety Oversight Board, and the charge that it's been given. And in showing you that charge, I'd like to ask you to just pay attention to the many bullets there. I'm going to come back to ask you a question about those at the end of my discussion. I'll then go into a summary of the meetings that have been held to date, extracting some of the larger themes that we've had, the themes that we've ended up discussing, and at the end, leading from themes into challenges, because I think one of the things that's emerged from the discussions we've had really is something that we're still grappling with, something that we're going to have to confront if this board is going to be effective the way Dr. von Eschenbach said he looked

for a board of this sort to be effective. So if I could have the next slide, please.

This slide comes from last spring's presentation, and it just outlines the people that are on the drug safety board. I am the chair at present. Susan Cummins is the executive director. In addition we have membership from the relevant CDER offices, especially the Office of New Drugs and the Office of Drug Safety, from Center for Biologics and Center for Devices and Radiological Health, and actually Miles Braun is one of the people that's the alternates there. From the NIH, and from the Veterans Administration hospital system. In addition, we've said that when necessary we would certainly involve consumer or patient representatives as we needed to get appropriate input.

The next slide is again from the last slide that you saw in the spring, and it says that the charge, the charge that we were given by the then commissioner to work under. What he asked us to do is provide independent oversight and advice to CDER center director on the management of important drug safety issues and policies, dissemination of certain safety information through FDA's website to health care professionals and patients. So in a very broad

sense to sort of watch over the way the center responded -- assessed, protected and responded to safety issues.

And the next two slides then take that one step further. And these are from the internal SOP, or the map we call it, that dictate how these boards function within an organization like CDER. And there were a total of seven activities that that map, that draft map I should say, identified as things the board should take under its purview. First, it suggested that the board identify, track and oversee management of important drug safety issues, similar to what we had said before; that the board adjudicate organizational disputes concerning management of drug safety issues; that the board select the drugs to be placed on Drug Watch, the website if you remember, and update their status on that website as appropriate; that the board establish policies regarding the management of drug safety issues in the Center for Drugs. Next slide, please. That the board oversee the development of patient professional information sheets. Again, these sheets would go up on the Web, so in a sense it follows on one of the other bullets. That we would track important emerging safety issues, and ensure that they are resolved in a timely manner.

Somewhat of an oversight function again. And then finally, to ensure that the CDER decisions about a drug's safety benefit from the input of external individuals such as the board members that we talked about. So a total of seven charges, fairly all of them important, all of them important to try to implement as quickly as we could. If I could have the next slide.

These are just the names of the individuals that have been hired since we last talked with you to help staff the board. All of them are high qualified, have a lot of expertise either in risk communication or previous work in safety matters. Their function at present has been to work with the center's divisions, the medical review divisions, to write the public health advisories when necessary, and to work with them to write the sheets that we would place on the website to inform patients and health care practitioners about emerging safety concerns.

So if I could move to the next slide, what I'd like to do is just, again, talk through some of the larger themes that I think have emerged from the four meetings that we've had to date. And they are didactic themes, things that we've done just in terms of talking to the members of the board so that they

understand the internal workings of the center better. Oversight of CDER safety issues, both in the pre-decisional, that is, recommendations made before the agency's had to make a final regulatory action, and post-decisional, looking back to give us input about a decision that's been reached, saying whether or not they agree that that was the best course to take. And then finally the thing that will lead into the challenges that I've identified is the policy develop conversations that we've had. I will say the discussion today will be limited somewhat by the commercial and confidential nature of some of the data used, but I'll obviously -- and everything that I will be talking about is available through other public means. So the next slide, please.

With regard to the didactic sessions, we've had to familiarize the members from outside CDER on several, you know, the important things about how CDER looks at safety so that they can give us better feedback. CDER's a very complex organization. It has a lot of parts, as Dr. Galson said, already engaged in looking at drug safety in the pre-marketing and the post-marketing venues. So these sessions have included discussions from the Office of Drug Safety and the Office of New Drugs about specifically how

they identify, track and monitor safety issues as they sort of bubble up out of the review or are identified in post-marketing adverse event reporting systems. We've also had a specific conversation, specific lecture from one of the members of the Office of Drug Safety on some of the recent guidances that have been put out to industry about how best to assess and address and detect safety issues, particularly in the post-marketing setting. Next, please.

With regards to the oversight of drug safety issues in a pre-decisional sense, I would say that the intent of the documents that were written, and I think the intent that we were given was to provide much material to the board, and in a common way ask them to give us information pre-decisional, that is, to really help us make decisions and then implement them. To do that we intended to be able to provide a full picture of the data as we knew it at that time, extensive background data in advance, presentations by knowledgeable senior review staff, and then solicit specific questions for actions, and then carry them out. Those pieces are still the way that we have handled the interactions with the board, still giving them a lot of extensive data, a lot of interaction with the relevant CDER staff. The

reality, however, has been that many of these safety issues are very time-sensitive. And so, it may happen on a Friday morning, and a decision is going to have to be made by, you know, Tuesday morning or something like that. And the board, it's just simply not possible to convene the board in that short a period of time. And so as a result, for some of these safety issues we've just had to limit the board's role to oversight after the decision has been made. For more complex, and for things that are obviously evolving over longer periods of time, it seemed terribly important for us to bring those things to the board. And we are -- one of the mechanisms we've done to sort of start doing this more often is to talk to the board about issues that we're not even sure are problems, really just they're issues that are being sort of followed throughout the center. And then as safety issues emerge we may be able to bring those things to them in a more effective and more time-sensitive manner. So next, please.

We have, however, had examples of oversight in a pre-decisional mode. And I'm going to talk about one particular example just to highlight, which was input that we saw from the board on transdermal patches containing fentanyl. As you know,

fentanyl's a terribly important product for pain control, particularly in patients who are not opiate-naïve, terribly important for patients with cancer and in other advanced pains. The issue was that through the Adverse Event Reporting System from the Office of Drug Safety had identified several patient deaths, and was concerned about possible fentanyl overdoses from these patches. And so we needed to confront what were the sources of those overdoses, and in fact that was where they were coming from, and whether or not there were risk management responses that CDER needed to take to try to minimize the chances of those happening. So what CDER did in advance of this meeting was to review the safety data, especially the post-marketing safety data from the Office of Drug Safety with an initial evaluation of the manufacturing and pharmacokinetic data to try to understand how these products are made, how they deliver the fentanyl, and whether there was anything about the way that was happening that might make patients at risk. And then finally, we had put out patient and health care practitioner sheets highlighting the need, the terribly important need to follow the labeling of these particular products very carefully and talk with physicians. The issue we took to the board, the thing

-- the decision that we really needed to ask the board about was what additional risk management tools did we need to think about to try to minimize the chances of these overdoses resulting in patient harm. Next, please.

This is just a cut-and-paste from what appeared on the proposed Drug Watch med list where we identified, we alerted patients and practitioners to be concerned about narcotic overdose and death. And what we said is just that we were looking into these reports, and that while we were looking at that it was very important to use these patches exactly as they were described, and that patients if at all possible should be talking to their physicians and making certain that they were using them appropriately. Next slide, please.

So with that in hand, we took that to the board. We said, here's what we have at present. What other steps do we need to take? What are the things that we need to think about doing? And the board had a different take than I would say some of us within CDER did. This was sort of -- it was an example of a place where we said something I guess, you always think you know what the answers might be. In this case the board said, boy, you've worked very hard,

you've got a lot of more work to do here. This is, you know, we're really very concerned about this. This is something where a full understanding, an absolutely integrated full understanding of the sources of the variability that was at least potentially being seen in how this drug was being delivered is essential. It's essential not only because the product has important therapeutic use, but it's essential because the products have very narrow therapeutic windows, and a small increase in the amount of drug that gets into a patient under the wrong circumstances could be very detrimental. So they said before you embark on risk management strategies, you really need to complete that evaluation, you need to complete it very thoroughly, and then come back to us and talk, and contemplate the use of things like medication guides, and other sort of management tools like that to really try to get a handle on the appropriate use of these products. And that particular action, an action of going back and looking in an integrated sense across all of the available data we have is currently at hand, and we're planning on bringing these products back to the board at the next meeting to give them what we have, and ask if we now have enough information for them to give us

some recommendations about additional risk management strategies. Next, please.

In a post-decisional sense, as I said, because of the time-sensitive nature of these we've ended up taking a lot of actions that the center has had to make back to the board to ask if we acted appropriately. And so one thing that we've ended up doing at the beginning of each of these meetings is reviewing all of the postings on the Drug Watch webpage. So any sheets that have gone up in the last six weeks or so, we send to the members of the board via MedWatch, we ask them, we talk through what the source of the webpage was, and ask them whether there are other things that they think we need to be doing about those particular safety issues. We also ask for feedback, obviously. And again, the feedback has been variable. Some cases, obviously that the board has felt that the actions have been appropriate, there haven't been other things that have been needed. There have, however, been occasions where their feedback has been quite clearly that we needed to think about other options, and I think that's been the most valued part of these discussions, has been when they suggested other courses that maybe CDER hadn't thought about, things that we hadn't had an

opportunity to do quite yet. And again, I think in the long run that has changed the way we thought about drug safety, the way we thought about approaching these things. It's been a really important part of this process.

The next slide just shows an example of that. And this is an example where at the end of the day the board in fact did agree with the decisions that we had made, but made one suggestion for us to follow on, and that had to do with the withdrawal of Palladone. Palladone is another product for patients with pain. In this case, it was a long-acting form of an opiate. And the issue was that when this product was taken with alcohol, it dose-dumped. All of the drug was lost from the extended release capsule very quickly, and the potential -- there could be potential for very serious consequences as a result. CDER had reviewed both in vitro, that is dumping it in the test tube, and in vivo, in human data, about the effects of using this drug with alcohol. And we had discussed alternative therapies, and there are alternative therapies available for this, obviously, that are not sustained release, and concluded that withdrawal of the product was in fact the best course forward. We had also started evaluation of other products that had

sustained release mechanisms to make certain that there weren't issues as well with them, obviously.

The board recommended that while the withdrawal of this product was appropriate, that we needed to have our chemistry and our manufacturing part of CDER implement a sort of standardized fashion in terms of how these kinds of products should be looked at prior to their approval. We needed to make certain that we were able to prevent this kind of thing from happening without us knowing about it in the future. And that's a thing that we've taken back. Our chemistry people are also working on those SOPs on the mechanisms whereby we assure that all reviews include a piece that asks about the effects of alcohol on the product. And we're planning on bringing that back to the board as well, sort of give them an update and say here's what we've accomplished, are there other things that you think that we need to do as well. Next, please.

The last thing, the last set of discussions I would say that we've had have been the most free-ranging, and maybe the hardest to capture on a slide, but they've been the policy things, the how do you implement a thing like an oversight board in a very complex organization like CDER, and how do you

make sure it's a success. How do you define success for a board of this nature. One of the first things that we asked the board to talk about is to define its role, because we thought that was terribly important, and obviously, as has been said before, it's very important to try to not reduplicate effort. In a time of constrained resources, if the board is doing things that other parts of the organization are already doing effectively, that's inefficient. There may be better ways to do that. Next, please.

One of the things we asked them to talk about was what threshold CDER should be using to decide when to communicate publicly about these emerging and important safety risks. The board grappled with that. They used some work examples. We presented three examples of things where we had chosen to put information into the public venue about a safety issue, or examples where we had chosen not to say something publicly at the time. We've sort of gone back from communicating an early safety issue, if you will. The board used those things to talk very broadly and identify the set of circumstances that could influence the need to say something public. And these are things that many other people have commented on, but included the gross credibility of the data

that we had in hand at the time we had to make this decision, the plausibility of the safety signal and its link to what the pharmacology of the drug was, relevant data that we had from other drugs, the severity and the reversibility of the adverse effect, and the public health impact of the adverse effect, if indeed it turned out that that adverse event was true, how much of a public impact that would have. We're planning on returning to this because we'd like to hone down this list. We'd like to be able to write some guidance to ourselves, internal guidance to ourselves, to really try to help guide decisions about whether or not to put information into the public venue by any one of these several communication means that Dr. Galson just went through. Next, please.

This was the challenge. This is the challenge I would say we are still facing for the board. And it is a policy issue as well. And it has to do with the oversight function. It's what I signaled at the beginning. What is effective oversight? How can we define when the board is successful, when it's, you know, it's achieved its function? We can tell Dr. Galson, in fact, that we're doing the job that he's asked us to do. And how does one conduct effective oversight? Again, this is a

very new group within the Center for Drugs. We don't typically look outside for advice the way this group does. It has a unique mix of expertise, drawing on people with very different backgrounds, people that are practicing physicians, people within the VA health system, people with a lot of expertise that we aren't typically able to draw on. It's important for this board to conduct its oversight over many, many groups in CDER, and those groups have very different goals, very different ways of working, and conducting oversight in that kind of an environment is sometimes challenging.

And finally, we need to do this in a timely manner. We need to implement -- these recommendations, if they're accepted by Dr. Galson, need to be implemented in a timely fashion. It's, you know, we understand that we don't have the luxury of time, and we need to be able to respond appropriately once a decision has been reached. We got a very long, very, again I'll say frank discussion about the need to do this. We need to confront this, we need to get this right. And the observation was made that in some sense this is going to make people uncomfortable. Pressing on a changing organization in this way is likely to be -- make people a little uneasy, and maybe

that's one of the things that we just need to expect. But as a start, what the board told us at the last meeting was they really needed to understand better all of the safety issues that CDER confronts, and understand better how those safety issues are being addressed. Next, please.

To do that, what we're planning on doing is bringing back to the board a canvass that we're conducting through the center to ask the center's vision directors to identify those safety issues that they see currently, to use that list in complement with the lists that the center already produces to identify and manage safety issues, lists that the Office of New Drugs creates, a list that the Office of Drug Safety creates, lists that other offices in the center create, to look at the totality of those data sources to ask are we tracking safety appropriately, are there other mechanisms we need, and then to use that discussion to translate the review into a clearer vision of how to conduct and implement safety oversight in the center.

Separately, we have started a quality systems approach to develop and track metrics of success for the board. This had been started prior to this conversation, and two meetings for this

particular initiative, this initiative of quality systems approach, have been held, and we're hoping to obtain additional comments at the upcoming Part 15 hearing, both with regards to how the board ought to be communicating with the external world, but also how we should be assuring that the board is successful in its objectives. Next, please.

So I'll summarize just by saying that the Drug Safety Oversight Board has a broad set of challenges that it's tasked with managing. All of them are important, and providing effective and timely oversight is a critical task that's been identified by the board, a task that we have to confront, we have to be able to address and work through appropriately. Board members are taking their responsibilities very seriously. It's been a real pleasure to chair these meetings. It's been wonderful even when conversations have gotten difficult. People have been very professional, and it's been a really refreshing place to be. New, fresh voices on safety in CDER I think are absolutely necessary. It's changed the tone of safety discussion at CDER, and I think it's changed that tone in a positive way. And to the specific, I think the presence of the board, the ability to ask the board for their help on these issues has changed

the approaches that CDER has taken on specific safety issues. I think that's been to the good. I think it's materially aided our work on drug safety. Next, please.

I'll close by just saying that I'd be happy to talk with anyone that has ideas or questions about anything that I said today. And then the next question, the next slide, please. I would like to ask, if the board is so inclined, to give us a little bit of feedback. I'd like you to give us some help. If based on your understanding about the safety system in the Center for Drugs, if you could help us prioritize those seven goals, those seven bullets that we were tasked with at the beginning of this, and whether some of them you view as higher priority than others. And Jan, if you can go one forward, I've placed the seven on a single slide here, if it's not too small. Again, these are the seven things that we had been tasked with trying to accomplish. And I thank you for your attention.

CHAIR SHINE: Thank you very much Doug. These two presentations are open for discussion. I would suggest with regard to the prioritization exercise, Jan, that if you will create a ballot, and we can sort of use a modified Delphi process by which

members can express their views after some discussion. Dr. Roses?

DR. ROSES: While I'm sympathetic to the way the issue of drug safety is being handled organizationally, I have an alternative view so that it would fit more into the Critical Path. Perhaps attaching more scientific view to the data on safety. Safety is a human problem. It creates patients. It creates patients with adverse events and side effects. The first thing that one would do in dealing with a disease, a new disease or a new syndrome, would not be to count it, but it would be to examine it, to get the patient's data to be as exact and as thorough as possible, which would include not just reports, but some active surveillance system. The data in and data out, and I don't need to go over the way that people talk about data coming in and data coming out. The fact is that if we're ever going to be in a position to effectively get effective and timely oversight of safety issues, and I'm using quotes here, and to not just -- and to find out that the adverse event is true, and to conduct effective oversight, we have to know what we're dealing with. And much more importantly than that, we have to know as early as possible what we can do to prevent it. All of that is

going to be coming not from simply dealing with reports, but putting together a system of surveillance which is active. Validating patients, validating the diagnosis and creating mechanisms with which to study and prevent safety issues. I think we've been grappling with this for a number of years, and it seems to me, and I hope the IOM was considering this, it would seem to me that the biggest change that's necessary is for active, not just post-marketing surveillance, but a marketing surveillance for any drug products and food products that are out there that present safety issues.

DR. CASSELL: Actually, I was having similar thoughts as Allen, but wondering in order to be able to do what Allen is suggesting, and given the, again, increased workload that I think FDA is being asked to do, I wonder about the information technology infrastructure, even personnel, that would allow you to do the kind of data mining that one would want to do. I think that to have the system, a proactive system of surveillance as Dr. Roses has suggested, and maybe Ken that would be one area that might be useful for us to better understand, perhaps at our next board meeting. It would be more about the IT infrastructure here at the agency. I don't know how people at the

agency would feel about that, or whether or not they think it would be helpful.

DR. GALSON: I'd just make one remark. We'd love to talk to you about that. We have a lot of exciting projects going on which I didn't have time to really go into that use information technology to improve how we communicate about risks, and also how we assess the information coming in, including some attempts to move towards a more active system. But, as you know, there are huge infrastructure challenges. We do have some funds, but they're very, very limited to do that, so it's definitely an area of large need, and we'd be happy to talk about that.

CHAIR SHINE: And actually, interactions between information technology not only in CDER, but in many other parts of the organization. So it's a good strategic area to think about.

DR. CASSELL: If I could just add one other thing. It occurs to me that FDA could provide a very valuable service in terms of not just helping to educate the public better about the role of FDA in drug approval, drug safety, etcetera, but going back to what Dr. von Eschenbach was talking about this morning about better informing the public about why they can go to sleep at night. And that is, would it

be possible, or maybe you already do this, to provide a speaker's bureau to medical schools to start in the first four years providing our up-and-coming physicians with information about how drugs are actually approved, the risk versus benefit issues, and more importantly the appropriateness of reporting adverse events, because I think this is still poorly understood, and I know, having served for six years on the LCME, the challenges in terms of even teaching pharmacology, much less, you know, getting at some of these issues. But if you had speakers that could go and maybe give special lectures it would be a good way to get information out. It would also be a good way to have people better understand what, you know, FDA is really all about.

DR. GALSON: No, I think those are excellent ideas. We've talked about those ideas and others that are very similar, and actually I'm sorry Scott Gottlieb isn't here, but this is one of the things that he's very, very interested in, and he's getting a group together in the agency to work on that idea plus other ways that we can communicate better with physician organizations that are very, very interested in the work.

CHAIR SHINE: In that regard, there are a

number of institutions that are now introducing fourth-year electives. Among those electives are intellectual property issues, technology transfer, and that would include this general agenda. It ought to be built into the curriculum. Dr. Harlander?

DR. HARLANDER: I guess my question is a follow-on to Gail's. Last night I was watching the news, and with the court decision on Vioxx there was a lot of interest and concern about drug safety, and yet no mention of the fact that, you know, in fact it was said that FDA's not doing anything about drug safety. So you know, is there a way, and do you have any kind of marketing plan to, you know, let the news media, the public, you know, patients know that these kinds of things now exist, and you know, what's happening. I didn't see anything in the presentations about Drug Watch, or you know, how are consumers going to get directed to this, or physicians get directed to this kind of information, and know that this is available to them.

DR. GALSON: I think even among our internal staff, not to speak of all the outside people, this is really the biggest complaint that people have, that we don't -- we're not successful in communicating not just specific information about

drugs, but the fact that we have a robust system that looks at drug safety, and that we respond, and that you know the innumerable press reports like, I didn't see the one you're talking about, but they're always wrong, almost always wrong, or they're missing big pieces of information. Again, I think this is something that Dr. Gottlieb is very interested in. He's hired a few people that are really specialists in how to communicate and work very closely on these issues with the press. I'm expecting that we will be able to do a better job of working with the press over the next few years, but the question about how we can do a better job of making sure the world out there is aware of what we're doing, again, is partially a resource challenge. The agency isn't really resourced well to do public information campaigns. We have a tiny, tiny budget for that. We tend -- we are able to leverage that very effectively. We have people who are good at getting, you know, free time in media outlets. But again, to really do a good job of this we have to work closely with professionals in risk communication, and that have some capacity to get the word out. And again that's a challenge that we are working on.

CHAIR SHINE: Specific thought -- you have

a lot of good information that's going on the webpage, but it's not going to be a very important source of disseminating information to people who don't go to the webpage. So the question is whether just as you do with JAMA and possibly Annals, where you have reports, where there are reports from CDC and so forth, could you reproduce the highlights of your webpage regularly in those journals? It might not cost you a lot. Consumers read the journals, and it might be a direct way to go from the webpage to the community. Cato?

DR. LAURENCIN: Well, thanks for the presentations by both of you. I thought they were very good. My question is how can this board, this Drug Safety Oversight Board, work more in the pre-decisional oversight manner rather than a post-decisional manner? Specifically, I counted 31 members on that board. There were about 14 alternative, but 31 members, which may make it a little bit unwieldy to be able to be involved in pre-decisional oversight. And in terms of some of the issues that we've seen that have come to the fore that FDA's been involved in, I think that the pre-decisional oversight becomes critical. Have you considered having a rapid response committee, or a rapid response group that can actually

get to with maybe five or six members who are committed to rapidly responding to issues that are coming about? I think that in terms of the public the issue is, of course, obviously is oversight, but it's also the level of response and the adequacy in terms of timing of response. And so the question is, number one, is that possible, have you thought about that.

Also, I haven't seen a schedule for the oversight board meetings. Are they monthly? Are they biweekly? What's the schedule for the next year? And how is that going to be communicated out?

DR. THROCKMORTON: Yes, I can comment on both of those. The schedule -- they've been meeting about every six weeks, has been the course. As far as the rapid response team, I didn't go into that and I probably should have. We do in fact have that set up. There is a -- in fact we can reach out to ask questions on Friday afternoon, the example that I used. I should have said something about that.

DR. LAURENCIN: And they can comment and make decisions on behalf of the entire board?

DR. THROCKMORTON: They make recommendations to Dr. Galson in the same way that the board makes recommendations to Dr. Galson, and then he chooses to accept them or not.

On the pre-marketing question, I want to make sure you understand this is the current system which is a major mechanism that we have set up to get peer review and outside input pre-marketing is our advisory committee system. And I think that that's working pretty well. The major impetus for forming the drug safety board was the post-marketing world. So, you know, it wouldn't be impossible for the board to get involved in a pre-marketing issue, but usually what happens is when we have a question that we think needs peer review or outside input we bring that to an advisory committee and time that so we can meet our review goals. So I'm not sure that there's a big need to get the board involved regularly in pre-market work, but it certainly could be done if there was something pressing that needed.

DR. RIVIERE: Is there a direct relationship between the drug safety advisory board and this current advisory committee, the drug safety board. It looks like you're covering some areas that, you know, there's a lot of people involved in both of those.

DR. GALSON: The advisory committee is all outside people. The Drug Safety Oversight Board is mostly inside people, with about I guess a quarter of

the people being from the outside.

DR. RIVIERE: I guess you indicated the pre- and post-marketing difference between them. It would seem that those two, at least the Drug Safety Advisory Committee, should be linked fairly closely to that advisory board.

DR. GALSON: In advisory -- I want to make sure we're not messing up on the nomenclature here -- we've got 20 different advisory committees that work on pre-marketing issues, both effectiveness and safety. We bring the drugs that pertain to those advisory committees to that specific advisory committee. There is also a risk management advisory committee. I don't know if that's the one you're talking about. And I think they really have a different role. The risk management advisory committee, again, is all outside people. We generally don't bring them specific drug issues, although we have. They're more about -- they've done more of their work on cross-cutting policy issues where they meet as a single board. We do invite members of that committee to the drug-specific advisory committees to help when there are those questions. So, yes, we do have a lot of different ways to seek this input. I think there have to be links made when they're working

on the same issue, but we think there's a lot of strength in the breadth of the outside.

CHAIR SHINE: Dr. Thomas?

DR. THOMAS: Yes, a question and a comment. How does the DSOB interface or relate to the generation of black box warnings and actual withdrawals?

DR. THROCKMORTON: They would be decisions -- those sorts of high-profile decisions were the ones that you would typically expect to come to the board. They are decisions in the same sense that any safety decision has the opportunity to come to the board if it's a thing that's obviously there's some organizational disputes. So there isn't a clear path forward. It's complex, or parts of the organization are disagreeing about what the best course is. Those things would come to the board in the same way that an issue that doesn't lead to a black box, doesn't lead to a warning. I would think things like withdrawals, things like that are really terribly important to get all the input you possibly can. If timing allows it I would imagine that asking the board about those kinds of decisions would be important. Again, a lot of times the withdrawals happen in relatively short periods of time because it's hard to involve the board

with their set schedule and things like that, but it's certainly an opportunity we'd probably use when we could.

DR. GALSON: One thing that a lot of people don't realize is that the size of the center, you know, 2,300 people or so, and the breadth of all of our work of generic drugs, over-the-counter drugs, and then all the prescription drugs. At any one moment, any one Friday, we have many dozens of pending important regulatory decisions that are taking place. So it's really not possible to involve the board in every one of these, and that was never the intent. It's really the ones that somehow get stuck, or are particularly contentious, or where there are groups within the center who are disagreeing. And if those are black box or withdrawal kinds of decisions then we would bring it to the Board or the emergency group if we could. But we can't bring everything, even the really important ones to the board, because of the time pressure, and the work load, and the fact that these people all have other jobs.

DR. THOMAS: I understand, thank you. The comment I have is sort of a follow-up to some remark earlier with regard to educating medical students or young physicians. Certainly you can go right down the

street to the ASPED offices and they have their annual meeting of all chairs of medical schools, or through the LCME or AMC as well. And just plant some seeds there. If you want to go international then go to IU Pharm because you've got all the pharmacology chairs and departments participating in those professional societies or groups.

DR. GALSON: We do some of this, but we don't do enough there's no question. There's broad recognition that we need to do more of this. Again, realize it takes people, because to send people to these meetings, it takes them away from their review jobs, and we have to have enough staff so that people can do this without feeling like they then have to go back and work all weekend and through Christmas.

CHAIR SHINE: I think we are going to be very interested in following up on the dissemination issue. This is a key issue. It's a large committee. I'd love to see an ethicist on this committee. There are ethicists at the NIH and elsewhere, given some of the judgment calls that have to be made about what you say when. I would just ask you to look at that as a possibility.

I think that we would be very interested to follow up, Steve, with regard to this whole issue

of safety as it relates to the use of genomics in evaluating drug effects. And as we've discussed before in this panel, what is the motivation interest of industry in characterizing those, what in fact is happening. Although we don't have time now to discuss that I think an update on that with regard to the tendency for pharma particularly to want to look for the largest market and therefore not necessarily segment markets is a challenge. And we will be interested in seeing what proportion of the black box and the withdrawals and so forth in fact come to this committee, and what role they play relatively speaking in terms of the overall activities with regard to drug safety. But thank you both for the presentation.

Janet Woodcock has been sitting very patiently here. Janet, we ran a little bit behind, but you've always been helpful in helping us keep up. Janet, as you know, is the Deputy Commissioner for Operations in the FDA, and she's going to give us an update on some of the FDA activities.

DR. WOODCOCK: Can you hear me? Can you hear me now in the back? Okay, good. Yes, I'll try to go through this quickly. We have brought many initiatives to the board over the past four years. Some of the new board members may not be familiar with

these. However, this is an update, a brief update, on where we are with a lot of those activities. So Jan can move to the next slide.

What I'm going to talk about, number one, is the Critical Path Initiative, number two, our efforts in pharmacogenomics, and number three, our progress in our manufacturing initiative. The Critical Path Initiative since the publication of our white paper about a year and a half ago it's been fairly quiet, but we've actually been making a considerable amount of progress. We have done extensive outreach and with a lot of scientists, and we've identified a lot of specific opportunities. And so we expect a second report from the Initiative to be out imminently. This will list many of the opportunities we've identified, and hopefully help stimulate additional research. We soon after that will put out a report that will describe the activities we're able to take on, either with partners or internally at the FDA, and it can match up with the list that we're going to issue. Next one.

We have been working in many areas. We have done a lot with the Interagency Oncology Task Force, with the National Cancer Institute in a lot of projects in cancer. And you're going to be hearing

more about that. We are working with NCI and CMS on a biomarker qualification initiative to look at in cancer, at cancer biomarkers. And more will come out about that soon. We have been working with freestanding academic institutes. Ray Woosley founded an institute in Tucson, the C-Path Institute, to work on Critical Path issues. It's a non-profit. He's putting together a group of collaborative activities, mainly from industry and FDA and other sectors to get some of the work done that we've identified. We're also talking to various universities. We had a workshop at Duke University on an ECG warehouse to start dealing with the problem of cardiac repolarization. And that's moving along quite well. We're also talking to UCSF and a number of other universities, and we have partnered with some industry partners to do CRADAs, to kind of do cooperative research agreements to kind of evaluate pathways forward. Next.

Examples of things that will come out under Critical Path. We did issue our final pharmacogenomic data submission guidance. I'm going to talk about that a little bit more. We issued a guidance on exploratory INDs. We had talked to the board about this. This is a way to do early sort of

pre-Phase I, or early Phase I studies in humans. That's gotten a very good reception from a wide variety of sectors, academic research community as well as the industry research community. We're evaluating the comments now. We expect to issue guidance, a matching guidance on GMPs for Phase I studies and manufacture of clinical supplies. And that's in the works.

We're planning a workshop on rapid microbial testing. We've done actually a lot of work behind the scenes on this to try and look at how can point-of-care microbial testing be developed. And we plan to issue a guidance fairly soon on the co-development of a drug and a pharmacogenomic test together for targeted therapy. And that will be a draft. Next.

We have done a lot in the bioinformatics area. Actually, part of what Steven was alluding to. I'm not going to go over these because of the shortness of time, but I will say we're working a lot on bioinformatics, and we just launched with the National Library of Medicine the Daily Med, which is going to be a national repository of all approved drug labels. And it's called the Daily Med because it'll be updated daily. And so it'll be real-time online.

And Ken, to your point, we expect that vendors will take this and push this information in targeted ways to people who wish to use it. And it'll be made available publicly, free, for that use. And I'm going to talk later this morning about our new initiative on regulation of clinical trials. Next.

So our next steps. We're going to publish this list in our report on our projects. We will be announcing, I believe, some consortia that are being formed to do some of the Critical Path projects. And these are I think significant. We can't talk about them yet in detail. And we're going to try to gather up a few more resources over the next year or so to get this work really moving within the agency. Next.

Now, as part of Critical Path really is a pharmacogenomics initiative. I think we -- that's moving along extremely well. Now, it's gotten kind of over its initial stage and is really into the stage where it's functioning very robustly. We issued our guidance on voluntary genomic data submission that we had first discussed with the board about a year and a half ago perhaps. We have an agency-wide pharmacogenomic review group up and running. They review all those voluntary submissions and share information across the agency. We've gotten almost 20

voluntary submissions from companies and various groups that are engaged in pharmacogenomics. We've gotten very positive feedback, both externally about the value of this as well as internally from our scientists across the agency. Next. Okay.

The framework for this whole program was provided by this first guidance. Next. The guidance introduced two novel tools. And we discussed with the board, because these were quite unusual for FDA. One was the Voluntary Genomic Data Submission where there would be submission of additional information that normally wouldn't have been required to be submitted to an IND and so it would be submitted outside that IND pathway. And it would not be used for regulatory decision-making, like microarray data, or data you didn't exactly know the meaning of yet. But it allowed the scientists, the industry and academic scientists, the FDA scientists to put their heads together, discuss these data and brainstorm about how it could be used in a development program of one type or another.

And then this IPRG is the Interdisciplinary Pharmacogenomics Review Group, a cross-agency, cross-disciplinary group that reviews these voluntary genomic data submissions, and now is

starting to represent the brain trust inside the agency on pharmacogenomics. And we're starting to -- there's starting to be a platform for our policy and guidance development in this area. Next. And we have a webpage for those of you who are deeply interested in this. Next.

So our milestones are listed here. In October we had our first large-scale toxicogenomics voluntary genomic data submission. This is a very interesting area. The FDA toxicologists have been telling me for a decade that there are better toxicology tests than what we currently do. And if there was only a concerted effort to pull this information together that we could in fact be a much better predictor of toxicology. The thing could be translated into human, what Allen was talking about I think, better monitoring or prediction of human reactions or organ toxicities. Nobody doubts this, it's just there hasn't been a mechanism to get this done. And so I think the ball is really rolling in this area, and the toxicogenomics is going to really develop over the next year or so.

In November we plan, the agency, the discuss pharmacogenomics at the International Conference on Harmonization, because this is obviously

a global issue that needs to be -- we've been talking to the international regulators about this. And I think that the U.S. FDA is ahead of most of the other agencies in our thinking on this. Okay, next.

So it's been very important for our scientists to see this cutting-edge genomic data as it develops so that by the time it's ready to be translated we're ready for it. It provides -- we're learning a lot as we brainstorm about this. For example, how to do these clinical trial designs incorporating pharmacogenomic data, and the review scientists in the review divisions, along with the cross-disciplinary team, are having a lot of conversations about this. Also, this allows us, as we had forecast, to do new policy development, because we're seeing this as it evolves, but before it hits the door as a formal submission. We have developed training sets of data to train reviewers so that they begin to understand what this data is actually going to look like, and we've gotten very positive feedback from sponsors, and they're coming in for more voluntary submissions, which means the experience wasn't too horrible. And if you recall, those of you who were here at the onset of this, one of the main barriers to industry using genomic technologies and

pharmacogenomics was the fear of interacting with the regulators. So I think this -- we have really helped put some of this to rest. Next one. Probably not with everybody, but with a lot of people.

We have learned that, as usual, that early communication is needed, and we're going to continue to need to build standards in this area. FDA doesn't necessarily create these standards, but if we can adopt voluntary standards, then that'll drive industry-wide adoption. We're going to have to train our reviewers, and we're rotating people into the multi-disciplinary review team so that they learn more about this, and the ICH is going to be very important as we start harmonizing internationally. Next.

So we have already had a joint voluntary submission meeting with the EMEA, the European regulatory agency. And we're working on an MOU with the EMEA on how we would do this, and keep all the data confidential amongst the parties. What we view now is we're going to have to have two expansions, okay? First would be the VXDS, which is expansion into other exploratory fields -omics, such as proteomics, metabolomics, and so forth. And the genomics was the most far advanced scientifically. We started there. The same conceptual framework can be

applied to these other technologies as they become more mature. So we'll be going in that direction. In addition, we're going to have to regulatory or required genomic data submissions at some point as this dream actually becomes a reality of actually using genomics to target therapy or to avoid toxicity. So it's very important for us, and contacts we've made also in the research community have spun off additional activities that are going to be very beneficial for this field. Next.

Also, FDA's approved three tests that can be used in pharmacogenomics, genetics really. These are three tests for drug metabolism, of variability. And these represent tools that can be applied in drug development or in the clinic to help keep people safer, actually, and make therapy more effective. Next.

Now, the National Center for Toxicologic Research at FDA has become very well integrated into all these activities. We have a robust research program in genomics, and so we have -- they're becoming a strong member of the team because of their laboratory and scientific expertise. They have also published quite a bit on bioinformatics approaches to analysis of microarray data. And so they're involved

in the standards activities. They also created a tool, the Array Track Software and Database that is, our reviewers say is excellent in assisting them in analyzing this mass of data when it's submitted. Next. So this Array Track is an integrated bioinformatics solution to manage analysis of microarray data. And we're training the FDA review staff. It's also available for the public, and it was developed at the National Center for Toxicologic Research at the FDA. Next.

And then, I'm not going to go over this in detail because of time constraints, but we're also participating in this project in QC metrics and microarray quality control. Obviously this is another set of standards that has to be developed so that we can rely on these data. We not only need a bioinformatics piece and the information transfer standards and so forth, we also need the analytical validation, the quality control piece, and that's what this project does. So Jan, if you can just go through those very quickly. There's more information available. Keep going through this. Yes. For those of you who are interested, these slides are available. Okay.

And then the final effort I wanted to

report on was the pharmaceutical GMP effort. We've been working with the Science Board for I think three years on this effort, since 2002. And just to update you, we've released seven guidances in this area, and we have chartered a Council on Pharmaceutical Quality, which is a cross-FDA council of all the groups that are involved in regulation of pharmaceutical quality. And that is functioning now very smoothly. Next one.

One of the guidances we introduced early is for process analytical technology. This has really taken off within the industry and within the scientific community, and the application of this PAT technology I think is really going to help transform the manufacturing of pharmaceuticals. And within a year we issued the Aseptic Processing Guidance, which we're trying to start harmonizing how we regulate aseptic processing internationally. We're working with NICH, and this was our effort to update those procedures. Next.

We also continue to work on our quality systems approach for industry. And we should be issuing a final on this pretty soon. We've issued a draft on comparability protocols. Jan, just keep going. We also are continuing to work on the Part 11, which is going to need a regulation change. And that

of course as you know is something that's fairly slow to happen. It takes a long time to rewrite a regulation. So we're working on that. Next one.

Recently the Center for Drugs announced that it's going to shift the way it does review of chemistry and manufacturing controls, the pre-market submissions in the manufacturing supplements. And this will be changed to a risk-based approach. They have to reorganize the teams, and a large workshop was recently held on this, and it'll be not the CMC anymore. It's Pharmaceutical Quality Assessment, and there will be different types of submissions by the industry that will focus more on how the formulation is developed, what information there is, what scientific information about the robustness of the formulation and the manufacturing process. So we've had a very large effort recently on that. The Office of Generic Drugs is also modifying its review system, and so hopefully some of the issues that were alluded to, say, by Dr. Throckmorton with alcohol effects and everything, we can make sure those are integrated into the review process. Jan, don't go to this one yet. The point of this, the importance of this is we believe this should reduce the need for manufacturers, if they submit the scientific information and the FDA

agrees with it, to submit manufacturing supplements, and be able to increase the number of first cycle approvals of a very high quality product at the end of the day in a more timely manner. So we believe that these changes will increase the quality of the submission, and of our review, and also improve timeliness, and decrease the number of supplements required. Next.

I'll have to skip over this, but we have done a lot of cross-cutting, both international and within the agency work, again, to make sure we have a consistent, high-quality regulatory program across all the different centers and entities, such as the fields that are involved. Next one. We have applied to the Pharmaceutical Inspection Cooperation Scheme, which is the -- it's the international group of inspectorates around the world. So we have all the different inspectorates from the different -- from developing countries and so forth there. We hope through that we can help influence and help harmonize how inspection is done around the world because the FDA inspectors cannot be everyplace all the time. And so we're continuing to work within the ICH as well. Next.

We are reevaluating our current regulations, GMP regulations, and after we complete

our assessment of what we want to do we'll probably talk to the Science Board about that at some point. And we also are establishing a pharmaceutical quality standards working group to determine how to better collaborate with the external standard pharmacopeias that are around the world.

So that's a brief update of many of the things that have been going on in these initiatives that we brought to the Science Board over the past several years. Thanks.

CHAIR SHINE: We have time for a few questions if the board wants to raise any issues. Just to clarify, Janet, you said there were 20 voluntary submissions of the genetic. What proportion of information -- what's the denominator for that. Secondly, what's the nature of the kinds of data that you get? Is it primarily related to toxicology, drug metabolism?

DR. WOODCOCK: Well, there is no denominator. This is a separate pathway, completely detached from the IND process. There are a very large number of INDs that are submitted to the several centers every year. So the voluntary submissions is a completely separate pathway. And we have 20 submissions. That's really all we can say about that.

The types of submissions are all over the place, toxicogenomics, efficacy, safety, not that much drug metabolism.

CHAIR SHINE: Who submits those 20? What's the basis for submission through that pathway?

DR. WOODCOCK: Anyone who's trying to develop a drug, a vaccine, or other product where they're doing genomic work, and they would like to discuss that with the agency outside of the regulatory process.

CHAIR SHINE: But ultimately the expectation is that some of those items --

DR. WOODCOCK: Absolutely, and that's where I was talking about the RGDS, the Required Genomic Data Submission. At some point, if the sponsor decides to integrate the genomics information into the development of the drug or vaccine or whatever, then they will have to come in through the regular process.

CHAIR SHINE: And the other question I have is with regard to good manufacturing processes, we talked a couple of times ago when we first approached this as to whether we could identify some benchmarks, or some parameters that could be followed in terms of whether -- you made reference in your

presentation that the industry thinks it can save money, or some portions of it. But we are very interested in would it decrease the number of lots recalled. Were there other measurable ways to see whether this in fact is useful? Where do we stand on that?

DR. WOODCOCK: We have struggled. We certainly took your comments to heart about metrics, and we have an evaluation group, and we have struggled with the evaluation of this effort. We believe -- it's hard to say what would have happened if you hadn't done something. For example, the trend on manufacturing supplements is now flat, where it had been going up. So we think we have decreased that tidal wave of filings that we had anticipated based on all the drugs that are approved, and all require supplements. As far as number of lots recalled or problems with the aseptic processing, for example, it's probably too soon to tell. Those data are extremely difficult to interpret. So we are really struggling with the proper metrics group success of this program still. We think the changes in the review side -- they will be much more amenable to measurement. As you know, one of the things that we've implemented is a risk model. This is the first

risk model that's been implemented in FDA as far as for inspections. It's a formal risk model that was developed with, you know, standard methodologies. As we start collecting more data that we can integrate into that model, that type of data will be the basis for the metrics that you're talking about.

CHAIR SHINE: Thank you. Any other questions? Yes, Gail, and then we need to take a break. All right, well let's do that. We're running a little bit behind, but let's take a 15-minute break, and we'll reconvene at 10 minutes of 11:00 promptly. Thank you.

(Whereupon, the foregoing matter went off the record at 10:36 a.m. and went back on the record at 10:57 a.m.).

CHAIR SHINE: Ladies and gentlemen, if we could reconvene. We're going to change the agenda a little bit because of the availability of presenters. And I would ask you, members of the committee, to turn to the report in your material on peer review of the ORA Pesticide Program. We're very grateful to Katherine Swanson and John Thomas who agreed to chair a small committee to do a peer review of that program, and they've provided what I think is a very comprehensive report. And we'll take it up right

after lunch since our speaker has returned. But I want you all to know it's a very good report.

We're going to go back to Janet Woodcock who's going to talk about bioresearch and monitoring. Janet, why don't you go ahead?

DR. WOODCOCK: Now? Thank you. I'm going to present a new initiative that the FDA has taken on called our Bioresearch Monitoring Initiative. And this involves an attempt to modernize the way we regulate our clinical trial process. Could I have the next?

We affectionately at the agency call this the BIMO program. A possibly unfortunate acronym, but that's the one we've used for a very long time. It stands for Bioresearch Monitoring, and it's a cross-cutting agency program that involves all centers, the Office of Regulatory Affairs, the Office of Chief Counsel, many people in the Office of Commissioner. This program sets standards in the area of expectations for how clinical trials are conducted in many aspects, performs inspections of clinical trials, makes sure they have been conducted appropriately. It has a review and enforcement component, along -- good laboratory practices, which are called GLPs. GLPs are for animal safety studies. It also has the standards

for good clinical practice, or GCPs, which have to do with all human studies. And this is all in respect to studies of FDA-regulated products. FDA doesn't regulate studies that don't involve FDA-regulated products in one was or another. The human subject protection piece of this is very closely associated with the BIMO program, although it's slightly different. We're also looking at our human subject protection oversight. The BIMO program accomplishes inspections of IRBs as part of the overall inspectional program that we conduct. Next.

The objectives of these programs are, number one, obviously primarily a huge objective is to protect human subjects in trials of FDA-regulated products. And I'm not going to talk anymore about the animal safety data, the GLPs, because we're not taking that up right now. So I'm going to focus on the human clinical trials. But a second and extremely important objective of the BIMO program is to ensure that there's high-quality data, and ensure the integrity of the data that's used to support marketing applications that are submitted to the FDA to support regulatory decision-making which forms actually the basis for our decision-making, and then actually eventually will provide the evidence base for the clinical use of most

of these regulated products once they get out onto the market. So integrity and quality of this data so that we can rely on it is extremely important, as well as of course protection of the subjects in the trials. Next.

Now we began this initiative internally in December of 2004. A steering committee charter has recently been approved by FDA management counsel. So after a period of fact-finding and so forth we become a formal steering committee overseeing this initiative. We are continuing right now to scope out dimensions, all the different issues that are current about human subject protection and clinical trial regulation, and we consider this part of our Critical Path Initiative, because modernization of this aspect of regulation is very important in moving forward. Next.

I'm chairing this along with David LePay who's the head of the central Good Clinical Practices Group at the agency. Rachel Behrman is scientific lead of this project, and the project manager is Terrie Crescenzi. And we have representatives across the agency. It was interesting, all the centers have some aspect of HSP and BIMO in their regulatory processes. Next one.

Obviously the BIMO program is very important. We have to make sure that trials are conducted properly. Even if informed consent is given properly, and the protocol appears on its face to be appropriate and ethical, you have to conduct the trials properly in order -- you have to make sure that actually they're implemented in a way that protects the subject. Trust and confidence in animal safety study results, and in clinical research, and even in the product development process itself is really dependent on the integrity of this clinical trial process and the supporting data. The regulatory program provides assurance of integrity, but if it is out of date it can actually inhibit innovation in the highest quality of clinical data. Ideally, our regulatory programs will facilitate the highest quality of clinical trial conduct and data. And the regulatory programs must modernize as the practices of clinical investigation change. So I'm going to give you some examples of how these practices have changed in the past several decades. Next.

We're seeing new trial methods and designs that actually were not contemplated back at the time when all these regulations and procedures were put into place. We're seeing new methods of data

collection and processing. In particular we're seeing electronic data capture. And we have been struggling for a number of years in trying to sort of retrofit our regulations, which were built for a paper-based approach to data collection and data maintenance, into the new electronic world. And there are a tremendous number of difficulties that we've encountered in doing that. This is an example. If we don't continue to innovate and provide modern standards, then the field may not be able to take advantage fully of electronic data capture, which actually has the potential of improving data quality remarkably. So we've got to do this.

Also, there are new arrangements between various sponsors among -- and various contractors. And so the research, we have the model would be a single small center contract with one or two universities, a PI at maybe one or two other universities to conduct a study, and that's how it would be done. Now we're seeing multiple, very large multiple-center trials, multiple contractors involved doing different pieces of the work, specialized laboratory testing, various other parts of the work. Of course, contract research organizations. Also, we're seeing different arrangements of IRBs than used

to be for-profit IRBs, central IRBs, all kind of different kind of IRBs, and the rise of free-standing for-profit study centers, where patients are studied, where that center exists mainly for the purpose of contracting and doing parts of clinical trials.

Nowadays, and this is good news, of course, but it also has to be conducted at the highest ethical standards, we're seeing a much greater number of studies in children and in other vulnerable populations as well. And it is good that we study people who need treatment so that we base their treatment on evidence, not extrapolation from other populations. On the other hand, this poses new challenges in how we actually conduct these studies, obtain consent and so forth.

There are many studies, and Allen and many people in this room know about this. There are many studies that use human -- repositories of human tissues and different things as part of their studies and so forth. This is another issue that has greater scrutiny now. Next.

Because of this retrofitting issue with our regulations, right now sponsors can delegate parts of the conduct of studies to parties that are not directly regulated by the FDA because we regulate the

investigator sponsor and so on, and those responsibilities are laid out in the regulations. And this has become somewhat problematic for us. We also see much more frequently very large trials, where this model of the single, look at the investigator, look at one or two investigators, and you've got a lot of the study, you understand the study, doesn't hold. The single site, any single site may only have a small contribution to the results. And here, the study-wide systems of data control and management are also very significant, and often aren't scrutinized in the same way.

As I said, centralized or for-profit IRBs is another evolving arrangement. We're also seeing globalization of clinical trials. Every year that becomes more frequent, and that's also good, of course, but it raises additional challenges. And we're seeing an increase in the number of trials of implanted or complex medical devices, and all the different type of issues they raise. These are different trials than the kind of trials we've done with therapeutics for a variety of reasons. Next.

So, does FDA's current regulatory program fit today's realities? That's what we're trying to find out in our initiative. And where we think

modernization may be needed, that's where we will concentrate our efforts. We're going to have to facilitate effective IRB oversight of this evolving clinical trial arena, to the extent FDA plays a role in this. And we have to facilitate IRB oversight of human subject protection, but we also have to make sure that our oversight over IRB function in trials of FDA-regulated products is everything it needs to be. We are going to have to provide regulatory guidance and possibly new regulatory scheme that encompasses the modern trial arrangements, and all the different parties who now are engaged in the conduct of clinical trials, and the care of patients in different settings within the trial. And also, another big need we've identified, we need common standards and regulatory requirements for electronic data handling, both domestic and internationally. We're going to have to have international harmonization on this point. Next.

So we're going to have to also be able to accommodate globalization of clinical trials based on a common standard and so forth. We must ensure a comprehensive approach to protection of vulnerable populations, and there are a number of activities that we're looking at, and pediatrics is one that's leading the way. We've been issuing guidances and draft rules

and so forth on pediatric protections. And we need to provide additional guidance to all parties regarding various procedures, all the special circumstances that now arise in today's trials, and we've heard that from a variety of the stakeholders. Next.

What are the internal challenges for our program right now? Well, it has been and is a highly decentralized function. There are units of varying size within the reviewing centers, within the centers. There's a field force that actually goes out and does the inspections, but they might have only a few experts in any given district in that particular function. And then there's a very small centralized group in the Office of the Commissioner. And that's how the function has worked over time. The environment is non-automated. Dr. Cassell asked earlier about databases and information technology. This is an area where we do not have databases that we need, and the kind of technology that would be helpful. And this area has also suffered from a lack of issuing a lot of guidance in the past. Whereas some development areas there has been a lot of guidance and standards, this has been lacking in that area. Next.

And an additional challenged as we scope

out our initiative is the multiplicity of stakeholders that we're going to have to consult. Because everybody kind of has to play on this. First of all, obviously primarily patients and people who volunteer, subjects in trials, and their doctors, investigators in the clinical research community. There are many things right now about how clinical research is done in the United States that impede efficient research. And probably the best quality data and so forth. And we need to do what we can, we think, to ameliorate this, but we're going to have to consult the investigators on what their issues are. Data managers. This is a group that we don't hear from much. They're in the back room managing the data. But this is a huge activity that goes on now that needs some more standards and discussion about how it's done. The industrial sponsors of all these trials are obviously stakeholders. And interestingly, the FDA review staff has a separate stakeholder from the BIMO program. The BIMO program is a compliance inspectional standard-setting. It's different than the review side, although the review activities also include a look at the data quality and integrity from a different perspective, and these two perspectives have to be put together. Then our compliance and

enforcement staff, because this program can be in cases an enforcement program. We can take civil or criminal actions at times against real outliers. And then HHS and other government agencies are also stakeholders here in various ways in the clinical trial arena. Next.

Now, what we've already identified, for example, is for the IRB system we need to modernize the way adverse events are reported to IRBs to accommodate the major trend towards multi-center trials. Right now are IRBs are getting -- they get all the different reports, the single reports from a multi-center trial involving hundreds of sites. And we had a Part 15 hearing on this last summer, and we heard from the IRB community that this is no way to analyze data. You can't make heads nor tails out of single reports that are rolling in. You don't have a denominator. You don't have any analysis of it. You just get all this stuff. So we need to help there.

The use of central IRBs. We issued a draft guidance awhile ago on using a centralized IRB process, and we are working to finish that guidance. And that sets forth some standards for a central IRB approach. Next. We also published some time ago a proposed rule on registration requirements for IRBs,

because they had -- we didn't have an inventory of all the IRBs, say, that were doing -- reviewing studies for FDA-regulated products. We're working with OHRP at the Department on this, and we're reviewing the comments to this rule, and hopefully we should get out a final rule in a fairly timely manner. We're also, as I said, finalizing an interim rule on safeguards for children in clinical trials of FDA-regulated products. And there are other rules and guidances in preparation I can't necessarily talk about that relate to areas we've identified that need evaluation. Next.

But also for the IRBs we need to optimize a more risk-based approach to our whole oversight of them. We need to look at the balance between real-time inspection of IRBs versus retrospective inspection at the time. We do both kinds of inspections. We might do retrospective after a study has been completed and sometime later go and look at the IRB. We probably -- we need a more risk-based algorithm such as we've developed for pharmaceutical manufacturing for targeting who we're going to go see. And we need better technology for tracking all this. Next.

Now, in the clinical trials area we of course have identified a number of issues and are

moving forward in some areas. We're finalizing a rule about foreign clinical studies not conducted under an IND. And this has to do with whether we can accept the foreign data, what are the parameters of accepting data that was generated in a different country, and not under an IND.

We plan to propose a rule on getting companies to report when they become aware of investigators who have falsified data, or potentially falsified data. This is a problem because one company may become aware of this. They may not tell anyone else, simply drop the investigator, who then may go on to be used by other sponsors. And we have seen this. People who tend to falsify data tend to do this in a serial fashion. And so we need to have everything possible in place to detect these people early, and take action against them. And we are developing and have in process a revised rule. This'll be a proposal on treatment use during an IND, and charging under an IND. Next.

We also are issuing guidance on use of data monitoring committees. Okay, that's a very big issue in the conduct of clinical trials, how to use these committees, who sees the data, and so forth. And this also relates to the function of the IRBs, and

what kind of reports do they get, and what do they learn about adverse events. The guidances on conduct of the clinical trials. As I said, this is an area where we haven't published that many guidances, and so we are developing guidances to put out. And then we're reviewing comments on a guidance we have on computerized systems used in clinical trials. As I said, this has been a very thorny issue because our current regulatory paradigm was based on the fact that you have paper records. Next.

Now, do I have a little bit of time? Okay, all right. I can go through this quickly, but I would like to talk a little bit about data quality, and what this really means, and some of the struggles that we've been having about this, and I'd be interested in getting your comments on it. We need a common definition of what "data quality" is. That's, again, that's something we don't have, is a consensus definition of what high-quality data might be. We also need some specific metrics, if you will, to assess whether the data are high quality or not. It's kind of been an "I know it when I see it" type of approach. And we need to assess the current system, that's what I've been talking about, for assuring data quality, to make sure it's up to date. And then we

think we need to put in a more continuous improvement model to get -- to keep modifying the regulation as the technology and the approaches continue to change in the clinical trial arena. Next.

Obviously as I already said we all, everyone engaged in this enterprise really shares the goal of generating high-quality clinical trial data. It isn't that people aren't trying, and it's very important for these reasons. Next. And the interesting thing about this, this is a shared responsibility amongst many parties. And wherever in the chain it breaks down, and we see it at every point, then you can run into problems, amongst all these different parties. Next.

For the investigator and the site, any given site of clinical research, the good clinical practices regulation and guidance embodies what you're supposed to do. And you are supposed to follow the protocol, and write down your observations and record them, and so forth, follow everything in the protocol. The study personnel here, and their training, and their quality is extremely important in this. And that's something that has been improved in the United States over the last decade or so, the quality of study personnel. But as more private practitioners

are being recruited into clinical trials, as clinical trials are moving out of traditional settings into other settings, here the site issue is an issue and perhaps an area of vulnerability. Next.

The sponsor needs to write study plans and protocols that are actually doable. And this is often where this breaks down, is to have a protocol that cannot actually be implemented. The sponsor also has to do investigator and site training to make sure they are able, capable of conducting the protocol. The sponsor is also responsible for something called monitoring your auditing study. And this is an area of evolution that we need to look into. The sponsors typically go to study sites every so often, every few weeks, or a month, or whatever, and make sure the study is being conducted correctly. And that is their quality control, and part of their quality assurance program. Other entities, some government entities that do trial and so forth do quality control and quality assurance quite differently. And we do not have a really comprehensive scheme about what are acceptable methods of monitoring quality or assuring quality by the sponsor, and the different ways you might accomplish the sort of performance objective.

And the sponsor also, and these data

people, do the data cleanup, a mysterious process, okay, whereby all this data is verified and made pretty perfect. We are going to talk to all the folks who are involved, using statisticians involved in processing data once it's generated -- entered in the case report forms, and talk about this step of the process. Next.

Now, the FDA oversees these clinical trials often while they're ongoing, during INDs or IDEs. Not always. And we also oversee the adverse events as they're unfolding. We do site inspections. That's part of, as I said, the bioresearch monitoring program is to go out and inspect the clinical trials. This is done fairly infrequently in real time, and more typically it's done well after the study has been completed, and the data have been submitted to the FDA. We also review the data that's submitted for validity. We issue guidance that tells investigators, tells sponsors, tells data people and so forth what the best practices are, what we think would be good standards to comply with. So developing standard is a very important role we have here. And then, as I said, we do enforcement activities, because there are people out there who will commit fraud, for example. Next.

Now we've identified an additional issue beyond all this, which is the automation and standardization means of this whole process. We have a rule, a Part 11 rule on electronic records. As I said in the GMP presentation, we're in the process of perhaps reevaluating that. But computer program validation and integrity is an extremely important part in the new electronic environment we're in. And then there's a whole piece of this. It is very, very clear that the whole field would benefit by a tremendous amount of standardization of how everything is done. This would really help the clinical investigators, for example, and study personnel. And so we are moving on many of these, and we've been working on these for a number of years, but we hope to increase our focus with this initiative. Next.

Now, this definition of high-quality data is very interesting. Many people have taken the tack that a hundred percent, okay? The hundred percent present would be high-quality. Others say fitness for use. Is it good enough for what you want to use it for? Others say you could write in your protocol how good you needed the data to be at the end of the day for various types of data in the protocol, and if it were that good then it would be good enough. We need

to at least explore these issues because this is not a trivial point, okay? We have to decide where data isn't of high quality, and we have to decide what we do about that, not on a case-by-case basis. We need a coherent framework to work from. It's clear that requiring 100 percent accurate data is an unrealistic requirement, but anything shy of that, I mean, how do you set the standard. And we would work with the review side of the FDA, the people who have to rely and use these data, as well as data -- people who manipulate the data to work through some of these issues. Next.

Now, any definition we have needs to incorporate certain considerations. We need to allow for risk management. In other words, if some information is collected and it's not very important, it probably shouldn't have the same level of scrutiny and requirements as the very important efficacy data or safety data points in the protocol. And one way that people have proposed doing this is doing sensitivity analysis and saying how much variability would be allowed before you'd really affect your conclusions, whatever conclusions you were drawing from that specific data analysis. And although that's a very good way to do it, that's also very

intellectually challenging and would be difficult to do on a routine basis. We know that all questions are not equally important, we know that. But can we develop a regulatory scheme that recognizes that, that has a risk-based approach.

Now, out in the real world, and you've probably heard this from us before, the definition of "quality" is different. It's meets the needs of the customer. Now you might say this operational definition of quality might, if you say it's adequate to the amount of variability will not affect the conclusions, and that might meet the needs of the customers. But this is another exercise we're going to have to go through to work on this. Next. Now, in the manufacturing world, not just your manufacturing pharmaceuticals, but anywhere, the operational definition of "quality" is that you've controlled variability to a certain level. That's the Six Sigma approach, for example. Believe me, we're not anywhere near that in the world of clinical medicine, and we're not going to get there very soon. So, acceptable variability differs by the use or the customer, which is really what I've been talking about, but you set specifications for that, and could this concept be applied then to clinical data and the amount of

variability is tolerable within the data. We're going to have to explore that.

Obviously there are trade-offs among efficiency, productivity and control of variability in anything that we're doing. And we need tools to assess this variability in data, statistical tools, so that we can apply more rigor to this rather than saying, well, it looks like there's too much risky data to me, or something like that. Next.

And generally quality is a system property. The retrospective review studies -- oh, okay. I'm done. I'm almost done. It's very difficult because you can't really put quality into a study once it's over. It has to be built in from the start. So that shows that really the good clinical practices, the training of the staff, the design of the protocol, all those things are among the most important things in ending up with high-quality data at the end of the day. And so what we have to deal with is what combination of education, guidance, collaboration with stakeholders, enforcement, inspection or whatever, would yield the best results. How do we manage this mix in a way, given our resources, that we get the best data out at the end of the day. Next.

So our job is to oversee the whole enterprise. Next. Just move on. And we think there are tremendous opportunities for improving the current system of data quality because the various industries spend a tremendous amount of effort on this, a very large number of resources. Nobody's really stepped back and examined this whole system, just things that could be adjusted. And we're going to have to include all these other stakeholders in the process, once we get to a point in our deliberations. Next.

Automation, standardization, common definitions, and a system-based approach we think are the tools that have the most promise. Next. We're going to continue to gather information. We're going to do these short-term deliverables, some of which we have in the pipeline now. We need to define where we want to go and then develop a longer-term plan for achieving that. And we will be conducting workshops and making other opportunities for public input as we move forward. I think that's it. Thank you.

CHAIR SHINE: Thank you very much.

(Applause)

CHAIR SHINE: I'll turn this open for questions, comments?

DR. MCNEIL: That was a great

presentation, Janet. I have one question going to the issue of multi-center trials with the potential for a small number of patients per site. I could imagine that would be come an increasing problem in the future, and here's my question. Suppose you have a site that has 20 patients for an, I don't know what the outcome is. I'm not talking about adverse events. I'm specifically talking about some outcome that you're looking for in the drug. And that drug has a lower apparent efficacy from that site than all of the others, but it's not statistically significant because it's too small and there's not even patients in that site. How do you deal with that? Do you do sensitivity analyses around it later? You can't just ignore the fact that consistently Hospital X is always worse.

DR. WOODCOCK: Right. We look at all that. In fact, we've had instances where in Europe the drug worked, a drug that didn't work in the U.S. and vice versa. And these are very difficult issues to deal with. Where if you took out a site and it still didn't affect the overall conclusions, then we tend to be -- and that's a kind of sensitivity analysis. We tend to be less concerned about it, although it does raise questions about what was going

on at that site. We might go in and inspect that site, for example. But these are the kind of statistical issues and practical issues that we'll be grappling with as we talk about data quality.

DR. MCNEIL: Allen mentioned that --

DR. WOODCOCK: Right.

DR. PI-SUNYER: Yes, I have a couple of questions and comments. It seems to me one of the issues related to the drift from academic centers to individual practitioners in terms of clinical research is related to a couple of things. One, central IRBs. I mean, it takes us two and a half months to get something through IRB. It takes a central CRO one week. And the companies are in a hurry. So I think that's become a real issue in terms of just signing up people.

Another problem that comes up with this shift is that the academic centers are asking for more and more in direct costs, whereas the individual practitioners are not. And if it increases the costs by 25 - 30 percent, then the drug company walks away from them and goes to individual practitioners. So these are issues that institutions really need to look at if they're going to continue in the clinical trials business.

The other issue that I think is really very important that you didn't even address is retention. I mean, I see these clinical trials with 50 percent retention at six months, and you don't know what happened to the other 50 percent of the people, and yet these are given as evidence that the drug is working all right. And so retention is a huge issue in many drug trials. It doesn't seem to be as much of an issue on NIH trials where they work harder at trying to keep retention of people. Maybe that has to do with they have more funds to do that, but it makes a huge difference. And in fact, the U.S. trials tend to be worse than the European trials in terms of retention as a group. So whether Americans are more fickle, or what it is, I don't know, but I think it is a huge problem.

DR. WOODCOCK: Well, it definitely is a problem. If you have a lot of dropouts in a trial it starts degrading the inferences that you can make from that trial, the statistical inferences you can make. We aren't putting that in the scope of the BIMO Initiative, although as you point out, perhaps some trial practices, there are some practices that can improve retention, and where it's related to practices in the trial that would be under the scope.

DR. SWANSON: The last two questions allude to a question that I had. Is there any attempt or initiative to look at international harmonization on some of these?

DR. WOODCOCK: Yes.

DR. THOMAS: Yes, a couple of comments and then a question. When you talk about high quality, I would suggest in your presentation you use the word "definitive endpoints" to be clear about endpoints, particularly when you're talking about multi sites because obviously it goes into a fair amount of time, but without definitive endpoints at the end of the day you have nothing.

The other thing is in terms of data cleanup, we've all had occasion to do that, but I think the agency should probably refer to it as something like "data review" or "reevaluation". There's a lot of elements of mischief involved in "data cleanup" to use that euphemism. You may want to coin a term.

The other comment relates to some of your earlier slides when you said you were developing guidelines, and maybe it's implicit, but I didn't see any designation for time frame, particularly as it relates to adverse events, and what is the thinking at

this point?

DR. WOODCOCK: I think what we concluded in the adverse event reporting to IRBs, is that what you're talking about? That we needed to do guidance, and then probably change the regulations to make them more clear. And of course, changing the regulations takes awhile. So that would be a long time frame, whereas guidance we can get out fairly quickly. And we're working on that right now.

DR. THOMAS: Present reports.

DR. WOODCOCK: Yes, well, what people were alluding to about the IRBs and the slowness, part of that is they're so over-burdened with these adverse event reports. And you know, so we need to do something about that quickly, and try to devise some approach that protects the subjects, allows the IRB to do their human subject protection function, gets them comprehensible information that they can use to make ethical decisions or decisions about risk.

And yes, I agree with you on the data cleanup piece. I mentioned it because we haven't worked on this, and so that's what people call it right now. Hopefully we'll develop some official government term for it and it'll become much better.

DR. CASSELL: Janet, you may be aware of

this. It's in the early stages, but I understand it's going quite well, and that is the Children's Health Information Initiative that's being led by Gail Mortenberg at CDC. Getting back to Dr. Eschenbach's idea about leveraging this morning, it occurred to me that because of the things you said particularly on the increase in numbers of studies on children, this may become quite valuable for a number of reasons. The original intent of this obviously relates to surveillance for infectious diseases and to be used in the event of a terrorist attack, but it could have multiple uses, especially if FDA could get involved and use it more as a database for drug surveillance.

DR. WOODCOCK: Thank you.

CHAIR SHINE: Let me make a couple of comments. First, language is important. A number of years ago an Institute of Medicine committee looking at clinical trials urged that we actually call them human participant protection programs. And the reason that they made that was, one, the pejorative notion of patients being subjects, or subjected to. Secondly that when we look at these programs, we need to look not just at the IRB, or not just at the data collection, but the overall program, including the environment in which it takes place, and so forth. So

this has implications in terms of the way we think about the role of the FDA in relation to other accreditors in terms of activity.

As you know, for 30 years we've been lamenting the loss of the clinical investigator, physician scientists and so forth who were doing these things, and for the first time in the last two or three years we actually see an increase in medical student interest in careers of this kind. And I think that the proliferation of programs in the K23, K24, K30 mode by the NIH has begun to increase interest. And so I'm very sensitive to the notion that we need to be very careful as we go through with these programs that we don't make them so complex, raise so many barriers or whatever that in fact we will once again discourage people from getting into these activities. At the same time, there's no question that FDA has a clear and major responsibility for the quality of these programs and the safety of the people that are involved. So it's really not a question of what our mission is, it's how we do it, and how we get it done best.

So some of my questions revolve around, for example, we are, in Texas we've developed, since we have multiple campuses, internal audit processes

for IRBs. We're encouraging all of our human participant programs to be accredited by either NCQA or its equivalent. It would be very helpful if in addition to dealing with all of the players in the field, we could try to figure out if there's any way that we can coordinate, integrate, or otherwise carry out these kinds of processes in such a way that we don't increase the administrative burden and regulatory burden for these activities, which are already, as you pointed on a number of occasions, really under enormous pressure. So I think trying to, for example, find a way to, for the sake of argument, emphasizing the critical nature of FDA on the data side, and the critical nature of some of the other accrediting bodies on the participant protection side, recognizing that there has to be some interaction on both sides may be a kind of strategy that would allow one to approach this in a way which is -- people throw up their hands as another set of obstacles that they have to jump over.

And finally, there are some, I think, pretty good paradigms around the country of really successful clinical research programs, including trials. Bill Crowley's program at MGH is a good example. And I would hope that as you go forward with

this activity, you look very carefully at in a well run program, how could you do what you need to do, again, without dramatically increasing the workload or making it look as if there's another great set of hurdles to cross. So I think this is an extremely important but very challenging area, as you've pointed out, and I just want to make a plea that with the recurrence of interest in some of these activities that we not throw cold water on it by the appearance that we've just made up a great deal more work for everybody to do, which has to get done in one way or another.

I think the quality issue is a fascinating issue, and I think, you know, as you have been doing, it's an area that deserves a significant amount of focused attention from a broad set of participants. And then, it would be very useful if that guidance could be used by other accrediting bodies so that when the NCQA comes in to look at a program, it's also checking on some of these. Just a few thoughts, but I congratulate you on trying to pull this together. Clearly you're going to be under increasing public scrutiny in this area, and anything that we can do to try to help with the interstices of this we'd be pleased to do. Thank you very much.

DR. WOODCOCK: Thank you. Yes, we'll be back to the Science Board as we move ahead on this. Thanks.

CHAIR SHINE: Ladies and gentlemen, we're running a little late, but for the Science Board Jan's going to tell us where to go to eat, and we're going to ask that we reconvene -- we have an opportunity for the public to comment at 12:30, so we really want to be back here at 12:30 to hear whatever public folks want to say. And we're going to go downstairs?

DR. JOHANNESSEN: Yes, downstairs. They should have a section for the Science Board down there.

CHAIR SHINE: We keep going in the --

DR. JOHANNESSEN: Yes.

CHAIR SHINE: Then let's reconvene at 12:30.

(Whereupon, the foregoing matter went off the record at 11:44 a.m. and went back on the record at 12:32 p.m.).

CHAIR SHINE: We have at least two individuals who have asked to make a statement. I would ask them to identify themselves, the organization which they represent, at the time they make their -- or I have to read something. Here I am

trying to expedite things.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it's important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship which you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any financial relationship. If you choose not to address this issue of financial relationships at the beginning of your

statement, it will not preclude you from speaking.

Anything else we need to read? Okay, good. I think our first presenter -- I'll try to do justice to pronunciation. Sadhana Dhruvakumar, who is I think also going to have some slides. Sadhana, would you go ahead?

DR. DHRUVAKUMAR: I wanted to start by saying that I have no financial relationships of the type that you described. My name is Sadhana Dhruvakumar and I'm a scientist with People for the Ethical Treatment of Animals. I did present to this group at the last meeting, and so I wanted to update you on PETA's activities since then in this realm, and also get a little bit more specific than the more general introduction I gave last time.

So I just wanted to start by recapping why we're interested in this issue. When it comes to animal experimentation, most of the tests out there have never been validated for human relevance, they're just presumed relevant, but if we put them through a rigorous process today they may -- we may find that

they are not. We don't find that they're reliably predictive of human responses due to species variation, disease models that aren't reflective, and physiological changes due to the laboratory environment. And especially at a point when we're speaking -- we just had a whole session about pharmacogenomics. When we're speaking about the differences between men and women, extrapolating from adults to children, or just between different individuals in the human species, trying to make that jump from another species is really logically inconsistent with that. So that's why we really want to make sure that research for drug research starts becoming more focused on human biology instead of animal biology.

The alternatives are things like in vitro technologies, genomics, early experimental medicines trials, epidemiology, bioinformatics. These are the future technologies that we see are going to be -- some of them are already developed. We're not saying that they're all there yet, but these are really

what's going to be the future of drug research.

In terms of PETA's activity since your last meeting, we have been deepening our relationship with the FDA. We have been presenting to various advisory committee meetings, attending different conferences such as the Science Forum, and we've had formal meetings with CDER very recently, and CBER in the Commissioner's office previous to that. So we're trying to get in there, learn and have introductory meetings, but more importantly identify specific opportunities for change, which are some of the things I'll talk to you about later. We've had similar meetings with the European Medicines Agency in London, and we're also applying to be an interested party, a formal interested party at the EMEA, which is similar to a stakeholder at the FDA.

We have been meeting with industry as well. We have been putting shareholder resolutions forth, and some of them have resulted in a dialogue with companies such as J&J, Schering Plough, and Medtronic. So we're starting these ongoing dialogues

with pharmaceutical companies who are the leaders in this type of field. We're going to the academic meetings in order to stay up to date on these latest alternative technologies. I wanted to especially point out the Fifth World Congress on Alternatives in Animal Use in Berlin has been growing rapidly, and there were almost a thousand scientists at this meeting. It's a growing field of its own. And with respect to the ICH, the International Conference on Harmonization, we've been making a lot of headway there. We have requested some kind of observership status there, and as we are, you know, moving towards that hopefully, we have been giving input on their activities. We have submitted a 14-page scientific comment on their draft guideline on the immunotoxicity studies, and a 5-page concept paper most recently on photo safety studies, harmonization between the regions, which has been quite well received and will be discussed at the ICH meeting in Chicago next week.

So now I wanted to get a bit more specific based on some of the work that I've been doing.

Rather than just talking about species differences, I wanted to get into why the species differences relate to a lack of human relevance. When you look at immune systems and immunotoxicity, and this is from some of the research for the ICH comments, for humans, the circulating leukocyte profile is 50 - 70 percent neutrophilic, but for rodents it is 50 - 100 percent lymphocytic. So when you have such a difference in the baseline -- one of the basic immunotoxicity tests is assessing drug-induced alterations in these subsets. But the baseline is so different that if you did see a difference it would be hard to tell what the human relevance would be of that difference.

Mouse spleens are major sites for life-long hematopoietic activity, while humans have virtually no hematopoietic activity in their spleens. So then when we use these mouse splenic cells as targets in our immunoassays, once again, the relevance is a little bit in doubt. And when you look at the actual functional differences, TCDD causes a dose dependent suppression of the T-cell dependent antibody

response in a certain strain of mice, but enhances that same response in two different strains of rats. So when you look at that kind of data, which of these is relevant to humans? It's really going to be guesswork, and the human might be a third situation altogether. So this is kind of drilling down a little bit into the specifics of where these species differences might lead us astray as we're trying to get to the human relevance.

And to use the example of cancer therapies, using animals as cancer models, naturally animal tumors are inherently very different from human tumors in how they behave. The rate of growth, the rate of aggression, the types of tumors, and the mechanisms that -- from which they arise. But putting aside naturally, the cancer that we induce in laboratory animals is through highly unnatural means. We're trying to get to a very quick cancer that is not really relevant to the way that cancer progresses in humans. So given that we study these types of models -- and another point is that metabolism is very

different between species, especially of toxic chemicals such as chemotherapeutic drugs as well as carcinogens. So we don't know that the animals are even seeing the same metabolites or the same chemicals. Given all of this, it's no wonder that we've cured mice of cancer for decades and it simply didn't work in humans, as Richard Klausner, former director of the NCI, once said.

So in terms of the FDA's Critical Path Initiative, that's really where we see this type of effort fitting. The white paper pointed out that 92 percent of drugs that pass pre-clinical testing, which is almost all in vivo animal-based testing now, fails during clinical trials, and we really need to modernize the criteria development path, which I see as a big part of that has to be to move from the animal models, not to better or different animal models, or transgenic models, but to non-animal, human-relevant, human biology-based models. Next slide, please.

Besides that, we actually have -- the FDA

has a legal mandate based on the ICCVAM Authorization Act of 2000. Each federal agency shall promote and encourage the development and use of alternatives to animal tests. So that is another reason why the FDA needs to be looking at these tests.

To get into very specific opportunities for replacement, this -- the rabies vaccine potency test is an example of at this stage it should be a pretty quick and easy win, but it's not. Routine batch testing of vaccines accounts for 20 percent of all animal use in biomedical research. So just this routine testing, which is one of the reasons why we're very interested in it, for rabies potency, 600 mice per batch are vaccinated and intracerebrally challenged with a live rabies vaccine. The control group, of course, dies of rabies, so it's a very painful and cruel test as well. But scientifically, a big problem with this test is the extremely high degree of variability, up to 400 percent. It's actually -- I've been to USDA meetings and FDA meetings where people have discussed this test, and

it's widely reviled. People don't trust it. Day to day your response will be different. There is a completely non-animal replacement test. There's the capture ELISA that directly measures the 3D protective antigen that is part of the rabies vaccine. So it's mechanistically-based. We understand the vaccine. We can measure for the protective antigen. CBER has worked on it in their labs. They consider it valid. The World Health Organization has had a couple of different workshops on it. But so far it has not made it into replacing the animal test in the books. And one of the reasons for that is that the NIH test itself is so variable that it's a moving target, and that's one of the problems of using animal tests as the gold standard against which we develop and measure these non-animal tests. So across the board right now we're currently still using the worst test, and we're not protecting humans as well as if we could use the better test which is in existence but is not put into the regulatory guidelines. Next slide.

When you look at carcinogenicity testing,

this is a much longer term endpoint for which we're not really there yet. But the same reasons that I just talked about for cancer, animal models of cancer being bad, is the same reasons obviously that carcinogenicity testing animals is also flawed. But on top of that the 2-year rodent cancer bioassay, which uses 200 rodents for studies -- it's a lifelong assay, is widely acknowledged to be very problematic. First of all it has a very high rate of false positive. Over 50 percent of chemicals appear as carcinogens in this test. And that is actually very problematic in this realm for drugs especially because some drugs that are actually very effective, such as PPAR agonists, are actually being pulled off the market. So people with diabetes can't get these drugs because they're rodent carcinogens. But we don't know if that relates to human carcinogenicity. In the meantime, people aren't getting their drugs. And also, each study takes three to five years to execute, and a million dollars, and people don't believe in the results anyway. So it's wildly problematic.

People have been criticizing this test for over 20 years, but in the last year there's been a significant ramp-up in the criticism of this test, so we're really hoping that this can lead to something where we can actually try to replace it. And the one thing I'd like to point out was that the E.U. has -- the European Center for the Validation of Alternative Methods has now two or three million Euro that they're devoting, starting now, to invalidating certain tests, especially animal tests. Basically they're going to put it through the same validation procedures that we use for the in vitro tests and see whether they hold up. And this is a process in really trying to measure these tests, and this test is one of their targets. So I think we're going to be seeing that this test is actually not valid. We're using an invalid test to try to protect people from cancer, but it's not good, it's not working.

In terms of in vitro alternatives, in vitro genotoxicity tests are already widely used, but that's only one part of the problem. Nongenotoxic

mechanisms of cancer need to be detected in other ways. There's cell transformation assays, which are -- some of them are currently subjects of OECD guidelines. So they're getting there as well, but we're going to need a whole battery of in vitro tests that includes genotoxicity, cell transformation, immunosuppression, hormone alteration. But once you have a battery, once you understand the various mechanisms of cancer development, this battery could replace the rodent bioassay. This would be a longer term project, but if we can get the FDA to define what it would accept as a battery, it will be easier for companies to work against this. This was actually one of the subjects of my meeting with CDER. I'm actually going to put together and propose a battery. And pharmaceutical companies as well have said to us this would really help us to know, because it's hard for us to develop these alternatives, not knowing how the FDA's going to view them at all. We don't want to make that investment. So if I can define this, I hope to present this to you next time and get CDER's input.

Then we can get companies working towards the replacement battery.

And I just wanted to also present a very exciting new technology called the Hurel Biochip. And PETA or myself is not in any way affiliated with this company, but it's been getting a lot of press. It's a whole different paradigm. It's kind of part of the new paradigm. These are biochips that are microfluidic circuits lined with cells from human organs. So you can create a circuit where the drug will see the different organs in the order that it would actually see them through the route of exposure, and it also re-circulates so that the metabolites from hitting one organ will go back and hit the other. So now you're getting a real simulation in a biochip on an extremely miniature scale of what might actually happen in a patient. And you know, you can use this to really look at interactions among tissue types and compounds. Also you can do multiple compounds, look at drug interactions. And in the future, if you could create these biochips based on actual patient's cells,

you would know how that patient will react to a given drug before they take it.

So in summary, I just want to give you a few thoughts to end up with. There's a lot of focus on drugs that are failing out there in the market, like Vioxx, but something like Vioxx, I think I've mentioned to you, was actually heart-healthy in animal trials. So that actually also represents a missed opportunity to spot safety at the pre-clinical stage. So people see Vioxx as a crisis, but I think that this 92 percent failure rate should also be seen as a crisis, even though it's a long-term underlying problem. So all the drug safety efforts that are going on right now, a lot of it is focused on post-marketing surveillance, but some of that effort really needs to be pushed back to the pre-clinical stage more than is going on.

A lot of the time we hear about animal tests, well, it's the best that we have at this time. But the more that we hear that mentality, it's complacency, it's there's no real reason to move on.

And it's just, we need to say that that's just not good enough, to say the best that we have at this time is what we'll use. I also hear sometimes specifically animal models that are known not to be working, people say, well, I'm still going to use it anyway. I'll get some information. It'll be better than getting no information at all. But actually, when you get that kind of information it's misleading. It's misinformation, and you're putting resources into doing an invalid animal test that could go towards getting to a better replacement.

In the long term, making tissue models more physiological is more feasible than making animals into humans, so that really has to be the route that we go to. They're not there yet, all the different in vitro models, but we need to put more effort into them. And you know, I think everyone believes that in 50 - 100 years, the way we do medicine is going to be very different than now, medical research, high-tech human biology-based effective methods will be there, and personalized

medicine, but we really need to start taking small concrete steps, such as the ones that I was trying to outline earlier, or else we won't get there in that time frame even. And that's it for me. Thank you.

CHAIR SHINE: Thank you very much. We have copies of the slides, and we'll have a hard copy of that for our record. Thank you very much. Is Susan Prolman here? Susan, would you please? Did you hear the original statement about identifying yourself? Okay. Whatever you like.

DR. PROLMAN: Hi, my name is Susan Prolman, and I should state at the outset that I have no financial relationships with any company that is, you know, would interact with the FDA or with this committee. I come here today representing both the Union of Concerned Scientists and also the Keep Antibiotics Working Coalition. The Union of Concerned Scientists operates a food and environment program, and we are dedicated to phasing out the routine non-therapeutic use of medically important antibiotics in livestock and poultry. Keep Antibiotics Working is a

coalition of health, environmental, consumer, human, and other advocacy groups, with a combined membership of nine million people. And Keep Antibiotics Working was formed to address the loss of antibiotic effectiveness as a result of overuse. And my comments today concern the FDA Science Board Advisory Committee's review of the National Antimicrobial Resistance Monitoring System, or NARMS.

My first point is that both the Union of Concerned Scientists and Keep Antibiotics Working very strongly support the work of NARMS. Antimicrobial resistance is a growing threat to public health, and NARMS is the primary tool within the United States Government for monitoring changes in antimicrobial resistance in food-borne pathogens. I'm sure folks know that NARMS is made up with three agencies working cooperatively together, the FDA, the USDA, and the CDC. We are very supportive of the surveillance and data collection currently being done. We think that NARMS would be even more useful if it were combined with a comprehensive government-collected data on drug

use in farm animals so that we can better understand the pressures leading to changes in resistance.

My second point today is that it is essential for the Science Board Advisory Committee to take this opportunity to state that USDA NARMS data must be adequate, and should be considered in public health surveillance and goal-setting. The Department of Health and Human Services is currently in the final stages of midterm review of the Healthy People 2010 Initiative. Keep Antibiotics Working and other public health advocates strongly objected to the proposed deletion from Healthy People 2010 of targets relating to resistance in salmonella slaughter isolates from cattle, swine and chicken. Unfortunately, we believe that this deletion is going to be accepted, and the USDA argued that this aspect of Healthy People 2010 should be deleted due to lack of data pertaining to salmonella species isolated from animals at slaughter. However, the FDA Center for Veterinary Medicine's website clearly states that the USDA is collecting this data as part of its NARMS work.

Animal isolates were included in NARMS because of the potential for antimicrobial drug use in animals to select for resistance, and because foods of animal origin are the most likely source of resistant food-borne pathogens, particularly in the case of salmonella. Salmonella is the second most common bacterial food-borne pathogen in the United States resulting in illness to more than a million people per year. The goal of the veterinary arm of NARMS is, quote, "To track the development of antimicrobial resistance in veterinary isolates as it arises, and disseminate information to all stakeholders in an attempt to arrest the development and spread of resistance, especially among food-borne pathogens," end quote.

We believe that the deletion of this aspect of Healthy People 2010 is a serious setback for public health. The USDA's position seems to be that although the agency is using public funds to conduct surveillance, the agency does not want this data to be used as a basis for taking the action to address the

problem being monitored. This is unacceptable. NARMS was created to monitor resistance to protect humans and animals. NARMS animal data must be adequate to be used in setting public health objectives. If it is not, the FDA Science Board Committee should ask how this surveillance and data collection can be improved to fulfill the stated mission, to track resistance in a manner that provides the public health benefit of detecting problems with resistance when they arise.

At this point I would like to request that the FDA Science Board Advisory Committee issue a public statement that the data the USDA collects is not valuable in itself unless it has public health implications, and that USDA must operate a program that is good enough for goal-setting. If the USDA does not intend its surveillance program to be used for goal-setting, then public funds should not be used for the collection of this data.

And third, I would like to comment that transparency and the opportunity for public review and participation are incredibly important in everything

that the FDA does related to public health, including the Science Board's review of NARMS. And I want to thank you very much for the opportunity to talk at this open public hearing today. And I would like to take this opportunity to request that full transcripts from the FDA's review of NARMS be made public. Thank you very much.

CHAIR SHINE: Thank you, Susan. The board will be looking at the report later in the day with regard to the peer review in the NARMS program. Is there any other public testimony? That concludes the public testimony. And we will move back to our agenda.

I made an effort to introduce this subject this morning when we looked like we were missing a speaker. But I would again want to thank Katherine Swanson, John Thomas and their colleagues for producing this review, which is included in your material, and ask them to proceed to tell us about the review and their major conclusions. After the presentation I'll ask members of the board to comment

on, clarify, whatever issues that you want to raise, and with the notion that the board will ultimately need to approve this report. We then may ask for any comments from FDA staff about the report, but it's our understanding that a formal response to the report will be made available at our next meeting, is that correct? So that there will be an in-depth response at that time. But I presume that Katherine's going to make the presentation.

DR. SWANSON: Yes, and thank you for that introduction. I hope that the board has had the opportunity to read the report. It is a draft. And we will be hopefully taking action on this today because we have spent a year working on this. If I can have the next slide, please.

Just to put it into context, you'll remember a year ago in November of 2004 the report that was done internally, the internal ORA Pesticide Peer Review report, was presented to this group. That report identified 18 management issues related to the pesticide program, and these are agricultural

pesticides. There were 21 science issues, and we were charged at that time to address that report. Next slide, please.

Fifteen key areas were identified in that internal report, including program management, laboratory science issues, productivity and timelines, resources that are available, and compliance with regulatory policy. And I should point out that on Page 14 of Appendix 2 in our report, we address each one of the 21 science-based issues in a summary format, and that provided the panel's response to these specific issues. But next slide.

We were asked to focus on science issues specifically related to sampling and methodology because these are very important issues obviously dealing with science. And so now what I'd like to do is go through what our external peer review found relative to the pesticide program. The peer review panel consisted of John Thomas and myself. We comfortable-chaired the panel. John asked me to present the report out in the interest of saving time,

but he is certainly going to help to answer any questions that might come up. We also had Joanne Cook, who is the Chief of the Bureau of Chemical Residue Labs from the State of Florida, as Florida has a very active pesticide program. Mark Lee, who is a research agricultural chemist from the Center of Analytical Chemistry in California was also involved. It was very important to have scientists who were actively engaged in pesticide residues on this panel. Steve Musser from CFSAN was also involved. He is the instrumentation and biophysics branch and the lead scientist for chemistry in CFSAN because they are also involved in pesticide work. But in addition to this, I do have to acknowledge Steve Robs and Lory Love who were our co-secretaries and helped us gather the information as well as John Marzilli.

The panel -- next slide please -- started, our process involved different site visits. We first went to Florida to get an understanding of what states are doing, because there is a lot of activity done in states with regard to pesticide residue analysis. We

had presentations there from members of the Florida State staff, as well as from FDA field staff so that we could understand the processes that they do. Next slide.

Our next visit was here in the Washington area in conjunction with one of our FDA board meetings, and we had CFSAN presentations and additional ORA presentations on the pesticide program. Next slide. We've concluded our work at a site visit in the FDA regional lab, where the analysis is done in California, and looked at the operation of the FDA pesticide lab. We had presentations from investigators and compliance officers as well as from the State of California's activities.

So I'll finish up with talking about each of the observations we had, and there'll be a series of slides of what our observations are, followed by our recommendations. First of all, FDA needs to clearly define the goals, requirements and desired outcomes for its pesticide program. I mean, this seems like an obvious observation, but the pesticide

program is not just something that occurs in the ORA group. It involves CFSAN. It involves CVM. It involves a number of different agencies. Considerations need to be given to globalization of the food supply, not just what occurs in the U.S., changes in pesticide usage that has occurred over time, consumers perception of risk, and changes in pesticide usage.

So the next slide, our recommendation includes -- there's a need for collaboration within FDA that would include CFSAN, CVM, and ORA, and other agencies, such as EPA, the USDA, and even states, in clearly defining what the goals of the ORA pesticide program should be. We acknowledge that there are a variety of different types of risks that are involved, and this is important to consider. There's the risk of violation. There's the risk to the public at large. There is risk to different subpopulations. And if we can get these organizations working together to articulate what the goals are, it will be a lot easier for ORA to understand why they are taking the

samples that they are.

The second recommendation is to implement a more effective information management system for sampling and methods. And we have some recommendations later on, but earlier there have been discussions about how is the information gathered, and this is a key need here.

Refocusing available resources to better mirror public health and safety interests is also important. And we'll get into that a little bit later on the no-tolerance pesticides. So there is a need to make sure that the resources that are being spent against pesticides are on those that really will have the biggest public health impact.

So that leads into the next slide, which is pesticide sampling should be risk-based. You know, it's not to say that risk isn't involved in the pesticide sampling. It certainly is. But there needs to be clear articulation of the types of risks that are being looked at. As I mentioned before, there's the risk to the public, which are the compounds that

might be impacting health. There's also the risk of a violation, because sometimes minor consumption commodities might contain a no-tolerance pesticide. We will get into that. There's also the risk to susceptible populations, such as children, etcetera. So next slide.

Our recommendations are ORA and CFSAN should jointly reevaluate the commodities that are to be sampled using a risk-based approach, and focus on the public health needs and also patterns of non-compliance. So they need to consider things like the volume of produce that might be imported, the availability of certain commodities in the regions where the samples are going on. The distribution, and what states might be looking at. For example, states might have a heavy sampling protocol, and instead of duplicating the efforts in a state that does have a strong pesticide program, perhaps they should be going into states that aren't sampling quite so frequently. There's also a need to look at severity when they're establishing these. And most importantly, communicate

to make sure that both organizations understand why these samples are being taken.

The third observation is related to the current sampling. Current sampling for pesticides is not statistically based. This might seem to be a shock, but the most important thing here is the very low incidence of finding a pesticide in commodities out there makes it almost impossible to have a feasible sampling plan that is statistically based, and this needs to be recognized. So our recommendations for this risk-based is, first, there needs to be an ongoing consultation with statisticians to make sure that they are involved in recommending a pesticide sampling program that will meet the defined goals of the pesticide sampling program. There also needs to be development of sampling plans that clearly articulate the data needs of the program and make sure that those needs are met.

Okay, so that leads us into Observation 4. We observed that there was a general lack of coordination between sample collection and analysis.

What happens is there is a listing of commodities that should be collected, and in some regions the people who collect the samples do not communicate to the lab to make sure that they are analyzed in a timely manner. In other regions, there is an attempt to make a coordinated effort. And so our recommendation related to this is to enhance the coordination that does exist to select the right samples and the timing of their collection so they can coordinate the analysis in an efficient manner in the laboratories. This requires communication between CFSAN, ORA, states, and other agencies to make sure that this is facilitated. There's also need to revitalize the pesticide coordination teams. In the past, these teams used to serve this function so there would be discussion about when samples are going to be collected. But as resources get thinner they get reallocated. And in retrospect, some type of coordination would definitely improve the analysis to make sure they come in at the right time, they get analyzed properly and the reports go out in a timely

manner.

Development of a notification process for scheduled sample submission is also important to enhance. And interaction between EPA and USDA to support risk assessment activities that they may have going on to make sure that we provide -- or FDA provides information on commodities that perhaps both EPA and USDA aren't sampling to balance the whole risk assessment effort.

I should note before moving on that these were our observations at the time that we did this peer review. However, it also should be noted that a lot of progress has been made already in coordinating these activities and timing the samples, and I don't want to suggest that improvements haven't been made.

So on to Observation 5. The Pesticide Analytical Manual, or PAM, is a document that contains the procedures that are used for analyzing for pesticides. This is a very important document. Not only is it used within the agency for conducting pesticides analysis, it's also used as a reference by

many foreign bodies as to what are some standards for pesticide analysis. And this manual needs to be updated in a timely manner because states use these procedures and international bodies use them as well. So our recommendations include that the PAM should be updated immediately to make sure that the most current methodologies are used. This does require resources, but in retrospect it will really help with moving the process along. There is need to create a process to get validated methodologies into PAM in a timely manner. Currently scientists don't have an incentive, Recommendation 3, to enter these validated methods into PAM. They have samples they need to analyze, but at the same time they should be getting these validated methodologies incorporated into PAM in a timely manner. Also, utilization of information from stakeholders and other experts in the field for editorial support might be an approach to avoid an undue burden on getting information into PAM in a timely manner.

So let's move on to Observation 6. There

should be a defined process for method validation and acceptance. Currently, validation is very important, and our recommendations include that there be a formal process for method validation. Each laboratory tends to approach this in a slightly different manner. Scientists have their way of approaching things, and there's a lot of intellectual desire to have their own way to do it. But if we can standardize an approach, it might facilitate getting validated methods into the PAM in a timely manner.

Then validated methods -- can we move to recommendations, please -- the use of validated methods for official regulatory samples is very necessary. And so if we can define a process for using methods for official samples that is obviously important, but as everybody knows, occasionally an emergency will arise, a new pesticide that perhaps a validated method doesn't exist, and we also need ways to analyze these samples in a timely manner and have a process for determining what are the key components of let's call it validation for emergency situations also

needs to be acknowledged.

We'll move on to Observation 7, and that is most methods that are used to analyze samples are generally cost-efficient and effective, but they may not be comprehensive. And this is an important consideration when you're looking at efficiency in moving samples through the lab. So as far as recommendations involving this observation, there is a need to harmonize methodology internationally, and efforts are going on in this particular situation, but we need to be looking for investigating alternative methodologies that are cost-effective, faster and more efficient, and these might include multi-residue screens. Everybody knows that methodology is improving very, very rapidly, and there are always new methods available. But if we could move toward expanding screening to LC/MS methodologies it would be better -- the agency would be better served. Too, looking at broader classes of residues that are out there they can detect residues that might be there more effectively, and this would help with efficiency.

So defining the pesticides' confirmation and quantification criteria is also needed.

There are international attempts to do this. State agencies, such as what we saw in Florida, do have standardized approaches. But right now we need to make sure that these get implemented within FDA, and there are efforts going forward to do that.

Let's get to Observation 8. This observation was the one that really provided most of the discussion for the panel, and we had to revisit it several times. And that is right now additional confirmation testing that is done on no-tolerance pesticides definitely increases the time and resource requirements that are going on in the ORA labs. Now, it's important to point out that there are a number of pesticides that may never be registered for a specific product because some of these products are not broadly consumed. Can we go to the next slide? For example, there are no commodities with EPA tolerance for commodities such as Chinese water chestnuts, for a fruit called a durian, for a variety of different

exotic fruits and things such as Chia Pet seeds. A manufacturer is not going to go through the expense to register claims with EPA for these kinds of commodities because they just aren't prevalent in the food supply. So presence of a no-tolerance pesticide is in fact a regulatory violation. However, it may not have a significant impact on public health, and this creates an issue. At the same time, CFSAN definitely requires confirmation and some estimate of the level of this pesticide for them to be able to take regulatory action. So we have a dichotomy here.

So what the committee is really suggesting is can we -- let's see, let's move to the recommendation. And that is if we can update the criteria that are required for analytical packages to support regulatory action for pesticides, including the no-tolerance pesticides, and we have them keep pace with new technology, then there are ways that we can come up with methodologies that would provide an estimate of the level that is there. And if these are validated, we can improve the turnaround time and

reduce the amount of effort that the analyst needs to do. Right now it's a very labor-intensive effort where it takes literally hours for the analyst to assemble these packages and put them together for regulatory action. So for example, using GCMS technology that provides both identity of the residue and an amount could be used as a screening test. And if that test has been validated and calibrated each time, that could provide a dual purpose where you're getting the estimate and a confirmation, and it can help with this requirement. I also have to admit for the record, I am a microbiologist and not an analytical chemist, and that might be obvious with some of my remarks right here.

So moving on to Observation 9. Uniform procedures for capturing, sharing, reporting, and auditing of raw data are lacking. And I think that this was evidence in, you know, the assembly of the information for packages for regulatory review, but there is an excessive time requirement to get all of the information assembled for the files. And so our

recommendation regarding this is really the agency should consider implementation of a more effective laboratory information management system, or a LIMS system, as rapidly as possible. And the fact of the matter is there are commercially available LIMS system that could be implemented fairly rapidly. We do not support development of an individual free-standing system, but rather looking at LIMS systems that could be applied across all laboratories for consistency and efficiency. And these LIMS systems actually do generate automatic reports, which would reduce analyst time and provide more consistency of the reports that are generated.

Moving on to Observation 10. Quality assurance programs are inconsistent across the ORA laboratories. It's understood that efforts for ISO certification or accreditation are in progress right now, and we strongly endorse continuing this progress, which is our first recommendation. We do hope that this -- recommendation slide, please -- so if we can complete that ISO accreditation, then there would be

standardization and collaboration across the laboratories on quality assurance policies and procedures so that we do have consistency there. We also recommend that there be introduction and augmentation of statistically based quality control procedures to reduce the unnecessary repetition in assaying samples. Next slide, please.

So in summary, we did have 10 recommendations, but really the overall finding is, again, there is great need for articulation and definition of what the goal of the ORA program, or the overall pesticide program within FDA needs to be clearly articulated, and there's need to improve the -- if that's articulated, then improvement in ORA's pesticide program will definitely occur. Next slide, please.

I really do -- John and I value the support that we got from the Bureau of Chemical Residue Laboratories from the Florida Department of Agriculture on Consumer Services. They provided a lot of input in our recommendations. FDA staff certainly

put in a lot of time and effort on this as well. The Pacific Regional Laboratory in Irvine helped us with many of our observations, and took time out of their busy schedules to show us what they were doing. And we were impressed, significantly impressed by the passion that people have around this project, the seriousness with which they are trying to do their job, and hopefully the board has additional information in the report for their consideration. We'd be happy to entertain any questions or clarification points that you have right now.

CHAIR SHINE: Thank you very much, Dr. Swanson. Dr. Thomas, would you like to?

DR. THOMAS: Very thorough report. I'm obviously biased. But to be sure I want to single out Jan and Norris for their support, along with I think Lory and Steve have already been mentioned. And we've probably overlooked someone, so I apologize for that.

And I'm also told that since we wrote the report that progress is being made with regard to the constituents on the editorial board of PAM, so that's

already moving along. I think some of the people at the FDA had the benefit of seeing the early drafts, and they got a jumpstart, and we're pleased to see that. That's excellent.

Couldn't emphasize more strongly the uniformity in reporting, and Katie has touched upon that. One of the newer challenges in the scientific vein is the entry of new biocides into the pesticide arena. When this program was brought into the agency many years ago we were really talking about two major chemical classes, the organophosphates and the organochlorines. That has changed drastically. Very few organochlorines type agents are used anymore, and there's been great restrictions on the organophosphates. But on the flip side of that it's opened up a whole new vista of different chemicals that have to be put into the libraries for analytical consideration and processing.

We did find an infinite amount of what I'll call wasted time in terms of the no-tolerance confirmatory process, which Katie alluded to. Somehow

we recognized that this is a regulatory, and there needs to be confirmation if for no other reason, legal purposes. But it does cause an inordinate amount of resources to be devoted to these confirmatory processes.

And finally, I should say, and again Katie touched on it, but there are some labs that have good quality assurance programs. Others are just getting involved in it.

CHAIR SHINE: Thank you, John. Are there questions, comments, from any members of the board? Anybody? Hearing none, I would like to entertain a motion to receive the report, and then before we vote on it, I'd like to ask John and our other members of the staff to comment with regard to what's happening. But this is their report, and so we're not going to rewrite the report per se. We may want the record to show that -- what's happened subsequently. Is there a motion?

DR. RIVIERE: I make a motion to receive the report.

DR. HARLANDER: Second.

CHAIR SHINE: It's been moved and seconded.

DR. MARZILLI: I'll defer to Bob in a minute, but I just wanted to say that this really has been an outstanding opportunity for all of FDA, not just the Office of Regulatory Affairs. And I think it's been an opportunity for our scientists and our investigators and inspectors in the field, as well as our colleagues in the Center for Food Safety and the Center for Veterinary Medicine to take a look at a program that's been a mainstay for the Food and Drug Administration for probably as long as the FDA's been around. I was down to our history office taking a look at some vintage photographs of FDA inspectors back in the 1930s, standing at the state line of specific states prohibiting certain fruit from crossing those lines because of the use of lead arsenate on those fruit products, and therefore stopping the interstate commerce of that particular product. And we no longer drive around in black

Studebakers and stand at state lines to enforce the work that we do, but I think this review has shown us that we're not alone in the work that we do. And it was great for our scientists in our six pesticide laboratories in the country to realize that they were a community of scientists doing this work together; that they had colleagues in the Center for Food Safety and the Center for Veterinary Medicine that were keenly interested in the work that they did, as was ORA senior management and the Science Board in bringing this forward. And it gave them an opportunity to have a forum to discuss some issues that have been underlying in our pesticide program for a good many years, and I think it's really reenergized the program.

The other thing it's done for us is really brought to light with our colleagues in the center that FDA is a part of the community of interest in this area; that we have colleagues at the U.S. Department of Agriculture that have a wealth of information that they are sharing with us through our

eLEXNET laboratory network system so that we're gaining all of this information in this day where information is the science that underlies the work that we do. We're also compiling data from our state colleagues, and it is an entire community of federal officials, state, and both federal agencies. And now with our colleagues from Mexico and Canada, we're really making it a community of interest across the North American continent.

It's been a great opportunity for ORA. Really what jumpstarted this for us was our meeting last spring with John and Katie, and interviewing our folks here in Rockville that really got folks working in earnest. And it's kind of jumpstarted the approach for us, because I think my colleagues at CFSAN and my folks at ORA headquarters, and in the field offices saw that the agency had interest in this program, and the agency wanted to make sure that we were being good stewards of our resources in doing the work that we do. So we're looking forward to the challenges laid ahead by the review board, and John and Katie, we

thank you for spending this time with us, and really the many, many days and hours of work that you put into this program shows the passion that you guys have for it as well, so I want to thank you, and I look forward to working with Dr. Brackett and his staff in really bringing our program into the 21st century.

DR. BRACKETT: Thank you, John. And I too would like to thank the committee for what I thought was a very thoughtful report, and something I think that was good for the agency overall to be focused on.

I would bring up three points I think that were part of it, and some of this was brought up by both Drs. Thomas and Swanson, one of which is the much closer need for coordination between not only just the field and the center, but also our state counterparts, and we are in fact trying to do that. And one of the priorities is to reinvigorate the pesticide coordination teams, because they did fulfill a very important function in the past, and they will in the future.

The second part is the importance of PAM

which we've realized, and of course as the microbiologists, the BAM, which is the microbiological counterpart, has the same impact, and it has languished over the years. And so consequently what we are in the process of doing is preparing procedures on how these methods will be added to PAM so it's not in an ad hoc manner, and providing protocols for validation of those particular methods. So it's quite important.

The third point I would like to bring out is one that was also important and that of statistical analysis, which is always a bugaboo for us. The one thing that I would ask you to keep in mind too, and Katie brought out the point, you know, why are we doing this. What is the purpose. The purpose is not to provide a baseline for pesticide content throughout the products. That we share with our states and the EPA. But I think we can be viewed more as a policeman function, which is we are taking spot checks to make sure that people are not in violation. And when our constituents know that, perhaps they will be less

likely to try to get around what we expect of them. But again, thank you very much.

CHAIR SHINE: Dr. Cassell?

DR. CASSELL: I just have two questions I wanted to ask John, really. What percent of our imported food products are screened for pesticides? And maybe that was said earlier on and I missed that. And the other question is how closely coordinated are your efforts with, say for example, CDC in communication of findings, particularly to the state and local health laboratories?

DR. MARZILLI: Okay, our findings are communicated normally through EPA and through our pesticide coordinators at the state level. The program itself has about 8,000 samples a year, of which about 80 percent of those are import samples. We tend to target problem product areas. In other words, if we find a particular commodity from a particular country that is more susceptible to pesticide abuse that we would then target that particular commodity from that country during that

growing season. Because as you know, we're receiving imports, particularly in the area of fresh produce, from all over the world 12 months a year. And our sampling program, as I said, if you're looking at 8,000 samples, and roughly 6,000 samples are samples of imported produce for pesticides from foreign countries, it's a small amount that we're sampling. When you look at the universe of imports coming into the country, there's something around 14 million entries a year, of all FDA-regulated products.

DR. CASSELL: Maybe one tenth of 1 percent it sounds like, which to me sounds pretty dangerous. Sorry, but it does. I mean, I think I remember after 9/11 hearing that with the increased funding for FDA you were able to go from screening 1 percent of our imported food products to 2 percent. But this is even screening far less than that for pesticide content.

DR. MARZILLI: True, it is a small number for pesticide content in particular, but one of the tools that we utilize is a system that we have in place of import alerts. And when we do find a problem

in a particular commodity area, we require that the importer ascertain a pesticide analysis, or a microbiological analysis of a particular product before we will permit importation. Because we simply can't be the policeman of all 14 million items being brought into the country, so when we find there's a violation rate, we move forward with an import alert. That's usually done in a pretty expedient fashion. Then the burden is on the importer to have that product analyzed and those results sent in to FDA.

DR. CASSELL: So what is your feeling? I mean, should there be a large increase in the percent that is being screened? I mean, should this committee say something about this? I mean, to me it sounds like an area that needs attention.

DR. MARZILLI: Again, you know, I would defer, you know, to the center in terms of the products, but we have to keep in mind that we have other large sampling efforts that are being conducted at the state level, because the states do analyze products coming into their laboratory, and we have a

large program within the U.S. Department of Agriculture. So it has to be the program in total, not just the FDA program. And I think that's what we're trying to do now with the approach that the board has given us.

DR. THOMAS: I just might complement what John said with respect to sampling, and things coming across the board. It's not possible to sample everything. That's a given. But recent legislation with respect to bioterrorism and things like that, you can stop ship before it gets to the dock. In yesteryear, apparently there was a person standing there with apples in his or her hand wanting to get into the United States, and now what do you do? Condemn the whole thing and send it back out in the ocean? At least there's some advance notice. And those are coordinated through the various offices. So, that's a step in the right direction, but it's never going to get to 100 percent sampling.

CHAIR SHINE: Any other comments? Hearing none I'll ask for a voice vote on acceptance of the

report. All in favor, aye? Opposed, no? Abstentions? The report is unanimously accepted. (A), we anticipate that four to six months from now we'll have a detailed response to the report. I would suggest, Bob, that in the course of that you might in fact give us an overview of how much testing is going on by whom in response to Dr. Cassell's question about what portion of the food supply is in fact being tested.

Again, I want to express my appreciation to Katherine and John. When I asked them to chair this activity they immediately responded. And clearly the quality of the report is outstanding, but I'd also remind the committee you're going to hear later about the National Antimicrobial Resistance Monitoring System. We are going to want to do an in-depth review of that. And I think the model of having a couple of members of the committee co-chair that with additional ad hoc experts is a pretty good model. So I hope other members of the committee will also step up to the plate in terms of the kind of job that Katherine

and -- or Katie and John performed.

Finally, before we go to the next session, as you know I always like to bring some literature to this group. There is an Israeli mystery writer named Batya Gur, G-U-R, who's written a whole series of mysteries that take place in Israel. One of them is called Murder on the Kibbutz. And it involves an accidental and a deliberate use of an organophosphate insecticide -- pesticide in the conduct of the murder. I recommendation it to you as both a good mystery and an opportunity to understand the risks of too close contact with pesticides.

With that, let's move on to a discussion of the Center for Devices and Radiological Health. This is a refreshing change of direction, Larry, because up to now we've been talking primarily about chemicals and drugs. The center's important activity, and Larry Kessler, the Director of the Office of Science and Engineering Laboratories in the center, is going to make a report on the prioritization process. Larry?

DR. KESSLER: Thanks, Dr. Shine. Sounds like I'm a little nervous -- pardon? Run them from there? That's fine. I'm nervous about the next piece of literature you bring. With the wide range of medical devices, I'm sure you could find several murder mysteries that would kill a lot of people with the right things in the device world, and I'll talk a little bit about that.

You probably want to get home. It's a Friday afternoon, it's a beautiful day, so I won't take too much of your time. Maybe 20 - 25 minutes chatting about what we call our science prioritization process, or a research prioritization process. I'll give you a little background about the office. Some of you know it so I apologize for being a little redundant. I'll talk a little bit about how we got there at the process itself, and some of the outcomes, because we just finished this year's prioritization process. Actually, we're in the midst of the finishing part of it, and also I'll describe that and how we're using it. So the next slide.

So, what do we do? Just a little background. What we think we do, and hopefully Dr. Schultz over there who is my boss agrees that we do this, we basically do three things in the Office of Science and Engineering Laboratories, four things. We do direct review of regulatory documents in consult with the rest of the Office of Device Evaluation, and the other parts of the center that do pre-market review. We also spend time developing generic techniques to enhance product safety and effectiveness. So we're doing lab work in order to help do the reviews, provide the scientific foundation and background for the work that we do in the pre- and post-market process. Now, I want to point out specifically the development of consensus standards here, because we spend quite a lot of time, not only in the Office of Science and Engineering Labs participating in consensus standards, but the whole center does that. And maybe at some other time we could talk about the fact that at least one-fourth of the entire Center for Devices and Radiological Health

is appointed to some national or international standards group around the world. It's a very effective way of doing a lot of the center's business. It's kind of a hidden aspect of the way device safety primarily works. So it's worth talking about, maybe at another meeting if Jan wants to schedule it. We also spend time, less so of course, doing scientific training for the regulatory staff, and finally both technical consultations inside and outside FDA. Next slide, Jan.

A little bit of logistics for you. We have buildings all over Rockville. We are spread out, like a lot of FDA is. We are looking forward to the White Oak campus. Half of the Life Science building at White Oak, the biology division is over there, and that's been very exciting, but it splits them up from us, 20 - 25 minutes away, and we are another 20 - 25 minutes from the pre- and post-markets up where Dr. Schultz lives. The size of the office, 175 staff, 36 contractors. And I will talk a little bit about the enormous range of devices that we cover, because you

get a picture that we've got 200 people covering a waterfront that a college of engineering would tend to cover. So it's quite a large arena.

And then finally, outside of salaries and indirect costs, just to give you guys a picture because some people don't have quite the understanding how we operate, basically our operating budget is less than $10,000 per person per year for all laboratory expenses. And then we have an extra $2,000 roughly for travel and training. So the laboratory budget is a little more than keeping the lights on, but not much. So if you want to do a study I've got the scientists paid for, I have his lab bench paid for, if he wants to buy reagents, if he wants to buy animals, if he wants to get a post doc, we have to figure out how to do it all out of a budget that's less than $10,000 per person per year. No laboratory that we've contacted has a budget that is at this level. Every other federal lab, even outside of NIH, EPA, NIOSH, the Armed Forces guys, they tend to be operating anywhere from $20,000 to $65,000 per person per year

when we count the same things. That is, take away salaries, take away travel and training. So we tend to operate at a fairly subsistence level. We do a lot of our work on a shoestring, and we do some by leveraging other organizations. I'm not going to talk about that today, but just to give you a picture that what we try to do is a whole lot with a whole lot of little. Next slide.

This is an idea of the range of products we have to cover. It's not just one area. So we're covering things that you would think of day in and day out are devices, like heart valves, or infusion pumps, or pacemakers, or implantable cardioverter defibrillators. But we also have to cover things like simple things, blood pressure cuffs in patient examination tables, biopsy devices and the whole range of in vitro diagnostic devices. So it's an enormous range of products. And when I talk about the divisions that are in the office, you'll get a picture, again, of how wide a range this is. Next slide.

How did we get to where we are today? Some of you may remember, most of you don't, in 2001 the whole center conducted a review under the Science Board auspices, and the whole center was looked at with respect to the total product lifecycle model. And in that review, I'm not going to talk about the bulk of the review, but in that review there were recommendations to what was then the Office of Science and Technology that we should perform a separate review of the office, increase involvement of the science folks in CDRH, focus our efforts on emerging science and technology, increase our knowledge-based documentation, and increase scientific collaboration with industry. So this was recommendations by this board approximately four years ago. Next slide.

So what did we do? I arrived as the Director of the Office of Science and Technology -- I had previously been the Director of the Office of Surveillance and Biometrics -- in the fall of 2002. And I established two goals for the office. After a couple of months I said these are the two things I

want to do, and if I can do these two things I'll be happy. But they're big things. The first is to chart a course to becoming an exciting and dynamic organization for cutting-edge regulatory research in medical devices. And second, make our office organizationally and the work we do integrated with the mission and function of the center. And this was a pretty big key. And I felt if we weren't doing this, we weren't doing our job, and if we weren't doing this, I wouldn't attract people who could do this, nor would it be a lot of fun. And if I'm not having fun I don't want the job. So that was basically what we decided to do. And it's a challenge because I'm trying to do it with 200 people covering a very large waterfront with no money, and trying to hire new people who are smart cookies to help us do this. It's a sort of a tough trick. I think we've done it but it has been a challenge. Next slide.

So in January 2003 I called together people from the Center for Devices and Radiological Health, people from the Center for Drugs and

Biologics, from NIST, from NIH, from others of our federal partners to come and look at our program. This was a federal review. Again, it was on the cheap. An NIH review would have been much more desirable, but didn't have $100,000 sitting around in my pocket to do this. So we did this on the cheap. Got what we thought was input from the rest of the agency as well as from outside, pretty talented people in the areas that we do work in, to look at our program, and look at what was 14 programs under the Office of Science and Technology at the time. And their recommendations were at least threefold. There were others, but the big ones were we should develop a protocol review and project prioritization system, because we had none. We should conduct an external science review, which we sort of blended into this, and change our organizational structure, and particularly focus on communication issues. Next slide.

So in 2004 we reorganized the office. Keep going. So the first thing we did is we

established a standards management staff, which we already had in place, which managed the standards efforts not only within the office but within the entire center. And then we split ourselves up in a different way into six divisions that I think you can recognize the work that's done. Prior titles were a little more confusing. I think this gives you a flavor what do we expect that we do in the Office of Science and Engineering Labs, which is what we changed our name to. We have a Division of Chemistry and Materials Sciences, and those guys basically do chemistry and materials science. There's no surprise there. We have a Division of Electronics and Software Engineering, a Division of Biology, Imaging and Applied Mathematics, Solid and Fluid Mechanics, and the Division of Physics. Now, those of you familiar with the physical sciences would look at the bottom three and say isn't this all physics? In a lot of ways I could have one big Division of Physics, but it would have been rather enormous and administratively unwieldy. So this is a slightly artificial carving up

of the world of physics, but these three areas, they work together and they also work independently so it works. And we have identifiable areas so that the rest of the Center for Devices as well as the rest of the agency, if they think they need help in imaging science, they know where to come. For example, we collaborate a whole lot with the imaging group and an imaging group in the Center for Drug Evaluation Research. They regulate contrast agents, there's a lot of imaging science that we work closely with CDER, and they know who we are because it says who we are, Division of Imaging and Applied Math. Next slide.

During the time we did the reorganization we began our science prioritization process. And it's undergone three iterations. I'll talk mostly about where we are today. We did it a little differently the first couple of years. But just this past month we've conducted the third round in the following way. The purpose of the prioritization process is to prioritize our activities to meet the center's and agency needs, and to enhance the scientific merit of

our work. And we believe the science prioritization process is the cornerstone of all science activities carried out in the office in support of the center's decision-making regulatory processes. Next slide.

The goals are to seek input from stakeholders in the center, FDA, and internal experts. We've increased the way we're doing that. I'll talk about that in a minute. Use the results for building a cutting-edge laboratory system, and develop new collaborations in part by leveraging the participation of our experts. So some people we bring in to evaluate our science are people we want to work with as well. Sounds a little incestuous. What it is. Next.

Here are the key components of the way we conduct the process. We prepare research proposals and they are reviewed by what's called a Technical Review Committee. The Technical Review Committee is made up of people from the Center for Devices, elsewhere in the agency, and now for the first time this year we've added faculty members, usually from

the FDA advisory boards that we empanel for evaluating devices. After the research proposals individually are reviewed, then they go up to the Science Prioritization Oversight Committee. It's a board basically of the deputy directors of the offices throughout the Center for Devices. So the head of pre-market, post-market, compliance, communication, education, radiation programs, etcetera, all re-vet the proposals at a lab level. More ultrasound, less photo sciences. More photo sciences, less radiation biology, etcetera, etcetera. The decisions come to me at some point. I'm the guy who's responsible. So while I very heavily rest on the advice I get from the both the technical review and the oversight committee, bottom line, I'm the office director, and I have to report to Dan and tell him what I'm doing, which are decisions as often as I can be consistent with these guys. When I'm not, I get to take the heat, so to speak.

And finally, the whole process is run by Subhas Malghan. Subhas, would you stand up back

there, because he worked really hard at this. It's a whole bunch of scientists who don't want to be reviewed who get reviewed, and he does all the arm-twisting. Usually I'm the bad cop. This is where he gets to be the bad cop. Once in awhile it's okay to be the director, so he's the bad cop. Next slide.

Here's what we've done this year. It's a little different. We reviewed our entire program two years ago, and it was very arduous. We've gone to a 3-year cycle. One-third of our labs have been reviewed, and we're doing it on a rolling cycle. And if you're going to interview and review a lab person in detail for hours, having to do that once a year is onerous. It just gets to feel onerous. We felt once every three years was a more reasonable time frame, especially because some of the projects really do have a 2- and 3-year cycle. Even though our budget is one year, we still think about cycles that are longer than that. This year we've included one academic member in each of the Technical Review Committees, and we complete the prioritization process in November so

that when the budget shows up this fall we're prepared to fund those projects that have risen to the top of the list, and modify and not fund those that struggled or got some sort of problems that we decided to go back to the drawing board. Next slide.

We reviewed six laboratories. I'll tell you about them in just a second. Four separate locations. We have five TRC members and an academician in each one of them. Next slide. So I'm going to talk to you about each lab that we reviewed, and just give you one example project so you have a flavor for what we're trying to cover.

The first one is ultrasound, the ultrasonics laboratory, and we were looking this year at a bunch of projects. One example is the evaluation of new thermal safety issues in medical ultrasound, in particular focusing on HIFU, high-frequency ultrasound, and its ability to generate relatively high energy, focused nicely but if you miss the mark what happens to tissue, what happens to the therapeutic intent of HIFU, etcetera. So we're doing

a study in that area.

This is an area that we've been studying for a long time and I don't think it's going to go away. This is electronic and wireless technologies. Medical device electromagnetic compatibility and wireless technologies. Wireless changes every couple of years. Three or four years ago we didn't have Bluetooth. Now we do. We could walk away from it and assume that everything we've done in other parts of the RF spectrum would work in terms of compatibility, but it just isn't so. So each year that the really splendid wireless world changes is time for us to re-gen up some projects, and take a look at how our compatibility issue is being handled. I have some really interesting stories in that arena if you want to talk details.

We reviewed our Radiation, Biology and Photo Sciences Program, and looked particularly at a project this year on ultraviolet radiation and skin color. A lot of the work that's done that relates to FDA, and not just the Center for Devices who regulate

UV-emitting and transmitting devices, but centers like the Center for Food Safety and Applied Nutrition. We worked closely with Dr. Kornhauser who works in CFSAN. They regulate products that modify or affect tanning, as does the Center for Drugs. So we're all in this together. And a lot of what's been done in Radiation, Biology and Photo Sciences is based on Caucasian Americans. We're now starting to do some of the first fundamental studies about how UV can be adapted to different skin colors. So it's kind of an interesting project. Next.

The next three, optimal diagnostics and therapeutics. We're looking at mechanisms of optimal spectroscopy-based diagnostic devices. We have a program both in diagnostic optics as well as therapeutics. Next. Electrical engineering. We've been looking for the last few years at pulse oximetry in the presence of motion. If you put pulse oximeters on, they're notorious for getting bad readings. They're worse when you have people how have tremors, clasping bed rails, etcetera. Trying to get a

standard developed for this has been a challenge. And finally, our cardiovascular interventional therapeutic program. A lot of work there is in pre-clinical large animal studies. We do studies that very few other people in the country do in pigs and in sheep here at the MOD II facility. We're very indebted to the Center for Veterinary Medicine for our collaboration with them. And one of the areas we've looked at were safety and effectiveness of emergent interventional therapeutics and delivery mechanisms for treatment of vascular disease and cancer. It's a big title, a lot of work, and John Karanian who heads that lab is here in the back if we have questions in that area. Next slide.

The basic processes of the Science Prioritization Program are a research proposal, lab description format, scoring by both the Technical Review Committee and the Science Prioritization Oversight Committee. Next slide. We standardized the description of the laboratory. That list, I'm not going to go over. Just to say that each laboratory we

try and lay out for both the technical committee and for the SPOC, the Science Prioritization Oversight Committee, what it is that they're supposed to see in the lab that they're looking for. Next slide.

We've standardized the research proposal contents. It's not based on, say, an NIH format because our regulatory needs would be a little different. So you have to focus not only on what is it you're trying to do, but really focus on the benefits of the center and their relationship with the center's strategic plan. What are we doing in the lab that matters? Sometimes it's hard to connect the dots. It's the one of the things that we were instructed to do. I think it's important to do. Next slide.

So I'll talk about the outcomes of the program. We have seen a direct change from having the rest of the center come and visit my lab folks, and look them in the eye, and ask them why they're doing what they're doing, and have that interaction back and forth between the laboratory people and the people who

take compliance actions, or the people who do pre-market reviews and ask why are we bothering with this. Why are we spending our precious few resources on some of the projects that I described. So that really has helped focus some of the regulatory needs, and in fact has allowed other parts of the center to raise their hand and say we have regulatory decision-oriented questions that we could use some help on. So that interchange has been developing over the last couple of years. It has been slow and painful, but we do believe we got increased buy-in from the center staff since more research is directed to the center's needs. We've transformed our projects, particularly not only in the publications, but in the standards and guidance documents. So a lot of times things might have sat in a publication, and now people are pushing them into standards and guidance documents, which is the way in which we help promote safety and effectiveness of products, and almost all of our products have undergone some changes based on comments from our regulatory partners. Next slide.

We've terminated or significantly redirected at least a dozen products over the last year and a half. Of roughly 75 projects that we are engaged in at any one time among the 200 laboratorians, we changed about 8 percent of them. Major funding and infrastructure decisions are based on this evaluation, and collaborations within each laboratory and other agencies have increased in order to accomplish some of the aims of the projects. Next slide.

So finally this is really a work in progress. This is the third iteration. We think we're closer to on-target than we've been before, but I'm sure by the next time we do this in a year from now there'll be some changes. We focused on high priority areas, and redirected research and time away from low priority based on this process. We've served as a cornerstone for all our budget and programmatic decisions, and we have increased, we believe, the center's -- not only just my office, but center staff ownership in the process, because they help the Office

of Science and Engineering Labs direct the research toward their high-priority needs.

It's been an interesting process. I can't thank my division directors who worked very hard to get their staff ready for it, and Dr. Malghan for running the program. I've had a lot of support from the front office staff from Dan Schultz, and appreciate your time and attention. Thank you very much.

CHAIR SHINE: Thank you very much. We have time for some questions, comments. Yes, Dr. Harlander?

DR. HARLANDER: I noticed that you terminated or changed the direction of 12 projects out of the 75 that you have. Do you have people then that are flexible enough to move into different programs? Or how do you manage that resource issue?

DR. KESSLER: Is this on or off the record? Do we have people who are flexible enough. Do you work in a LISRICS lab? Okay, so you know the answer to that question, right? So here's the answer.

To some degree yes. One of the reasons we restructured the office, we looked a little bit like the rest of the center. We were division, branch, etcetera. I abolished the branches, so we have basically around 20 laboratories. I have a laboratory leader in each group. So if one of his or her projects goes down the tubes, it's his or her job to take that person and some of their time, redirect them, put them on a different project, have them do retraining, maybe send them on detail up to, say, the Office of Compliance or Device Evaluation for some work with the rest of the center to bring back a more useful project. So some of them are flexible. Some of them have not been very happy, and they've been not so very flexible. But generally, we've had to move some people around. I'd say we're canceling a small number of projects, redirecting people more, and just sort of pushing the buttons to say you got a review from these folks. They told you what you're doing is not worthwhile for the rest of the center. Come back and tell me how you're going to change it and make it

so. And that's put them under a lot of pressure.

DR. HARLANDER: And does your review include a budget review as well?

DR. KESSLER: Yes. But at a fairly high level. The rest of the center -- I'll say this delicately. With all due respect, the rest of the center has very little experience in either running or performing laboratory research. So their ability to tell me whether I need a new atomic force microscope at $175,000, whether animals should or shouldn't cost in husbandry fees, you know, $2.00 per rat per day, whether that's a good or a bad buy, they don't know. I can't ask them to do that. Asking them basically for a fairly high level would be putting a significant amount of resources into this or not, and give them a picture of how many FTEs, it is, that's a feel I think they can get. If we're talking about two or three full-time equivalents, if they feel that's adequate or not. But below that, I would ask them to micromanage something they'd be incapable of doing, and I don't want to ask them to do that. Because I'm talking

about people who are engineers, pathologists, review scientists, some of them are even lawyers and statisticians. Their budget handle on lab stuff is not really very acute.

CHAIR SHINE: Dr. Thomas?

DR. THOMAS: Yes, I want to follow up on your review process. You said you implemented that in the last year or two. And you review a third of them. Do you review at the beginning in the project, the middle, or the end?

DR. KESSLER: We try to review at the beginning before we start. Because we're on a 3-year cycle and we're just starting, a few of the projects have already been going on. And so we're starting in the middle in a few cases.

DR. THOMAS: So you're really reviewing a proposal as opposed to progress?

DR. KESSLER: Generally a proposal as opposed to progress. There are a few cases, because there will be a track record, and John could speak to this, a lot of the work he's doing in interventional

science has been going on for the past four or five years, John, is that fair? So we're in the middle. But what we've done is say here's the proposal for this project, give them background. If at that point they think we need redirection, you know, it'll cause a hiccup, but that's the way we'll have to go.

DR. THOMAS: And does your unit have any sort of policy with regard to canceling a project outright, or any provisions for, say, a one-year extension? Assuming you're getting some exciting data.

DR. KESSLER: Well, if we're getting exciting data, again, it's my call. I'll let something go even if the rest of the center thinks it's not great. But I've canceled projects flat out. It's not been fun. I buy Kleenex, you know, by the bucket-load when that happens because I have scientists who've been told -- this is hard to say, but I've had to look a couple of people in the eye and say I'm sorry about the research you've done for the last 10 years and you want to keep doing it. You're

not going to keep doing it.

And I'll give you a good example of a success and tell you what it means. Some of you may or may not know the history of natural rubber latex in the Center for Devices. But latex allergies is a big deal. We've discovered roughly 10 - 12 years something, a phenomenon that didn't exist before, and there's a lot of history to it. Maybe it's 15 years. Some of the lab people in Dr. Lightfoot's laboratory spent about 10 years researching various aspects of how this thing works. And I think we've done an outstanding job. I think the track record that we have for proving and analyzing natural rubber latex in the lab has been pretty impressive. But a year or so ago when we were working on what I felt was the third and fourth decimal of this problem, we went to those lab people and said been there, done that, you've done it for 10 years, we think we've made a lot of progress. The rest of the job is now in the regulatory world to change the way in which powder is on latex gloves or not, and we're not going to do

that. We've redirected that. That person is now doing toxicological studies of nanoparticles. We said no more natural rubber latex. Find something else. This person spent a year roughly -- is that about right, Marilyn? -- researching where she could put her toxicological skills, and now her time is primarily spent in looking at we think emerging problems potentially in toxicology and nanoparticles. And those are going to affect the Center for Devices. So that's the way we've moved. Fair? Does that help you?

DR. THOMAS: Yes, just one quick follow-up. I would urge some caution when you tell me that you have some of your chief investigators who come from different backgrounds, and you're not requiring them to put together a full proposal. I understand somebody at some point in time has to make the decision on a very expensive piece of instrumentation, but I think the principal investigator should have an appreciation for some sort of budgetary considerations. You left me with the impression that

you were divorcing some of those things.

DR. KESSLER: No, no, no. Every proposal has budgetary stuff, etcetera. It's the evaluation of it. I'm not asking the rest of the center to look at, you know, the little dollars and cents.

DR. THOMAS: Okay.

DR. KESSLER: Every proposal has a budget, every PI has to put together a full proposal. How many pages are they on average, Subhas? Eight to ten. With budget? Three-year budget proposals. To be consistent with the 3-year review. So I've given you a misimpression. I apologize. Dan? Turn your mic on. The little red thing will show up. He's a surgeon.

DR. SCHULTZ: I was just saying, try to explain how you explain Beowulf to the center staff as an example of why we don't go into some great detail.

DR. KESSLER: For our imaging group we published -- we purchased a very large computer cluster that's a Beowulf system to do heavy-duty mathematical analyses of imaging. And we had the

entire center staff come over and view the whole boxes, which is really pretty exciting for a lawyer and for a regulatory scientist, and then walked through with them the imaging science that would have to be done. We spent probably about an hour walking through the various projects that we do. So I try to give the rest of the center an appreciation of what we do even outside the technical review committees.

CHAIR SHINE: Larry, this may overlap, or does overlap with a lot of other activities in the center, but I have two questions. One is you talked about consensus standards, and the role in dealing with those. At the present time, if I'm a device developer, or a device manufacturer, and I have a piece of equipment that I'm trying to develop at my cardiologist, or maybe it's a new heart valve, or a new defibrillator, or whatever, can I go to you and get a fairly clear notion from a regulatory point of view what standards I will have to meet in terms of my -- the assessment of that particular piece of equipment in a way that's clear so that when I get

through with that evaluation somebody's not going to tell me, yes, but we need to do this too.

DR. KESSLER: That's your first question? Do you want me to answer that before your second?

CHAIR SHINE: Yes, I'd be interested.

DR. KESSLER: The answer is basically yes. And I'm a good scientist, so I'm not going to just say yes or no. I'll give you an explanation. If you're making a new device, and you want to find out how the standards world might apply to the way in which you produce that device and bring it to us, one of the things you would do is look to the center for two things. You would look to see if there are guidance documents that exist already, or you would go to our website and look at -- we have a website under the standards program of the 670 recognized international standards that apply to devices. And those recognized standards actually allow you as a manufacturer to come through the regulatory process a little smoother than if you were inventing everything on your own and not using those standards. So if you

make a heart valve, and you want to use, we'll say, a mechanical heart valve with certain kinds of metallic equipment, you could look under heart valve standards, see what applies. And if we've already recognized a strength standard, material standard, a wearability standard, be able to look at that, might be ISO, might be IEC, International Electrotechnical Commission, pull that standard. Manufacturers tend to have to buy them. Pull them off the Web, look at them and apply them in your manufacturing process. And then we have, and Dan can speak to this, different regulatory mechanisms that allow you to come through the system, and in certain cases you can send in a very abbreviated 510(k), or abbreviated submission to us, say I'm citing international standards, and I have in my master file the fact that we have obeyed all the letter and spirit of the law of each of these regulatory standards that helps our reviewers slip through the system. I mean, the whole product can be done that way.

However, it's not uniform. There are

certain areas where the standards world -- orthopedics is a good example -- is way ahead of the game, and others, like anesthesia, which are creeping up to get caught up. So it depends on your product. If you're making orthopedic product, the standards are in terrific shape. If you're making anesthesia product, it's emerging. If you're making a closed loop product, meaning a product that would both diagnose and then treat a patient. So for example, an implanted glucose meter that detects where you are in your diabetic insulin routine and then would administer the insulin without your having to be involved, they're actually inventing these things. That's a closed loop system, and the standards world is just starting to deal with those. So it depends on your product. But there are certain products where absolutely we have two types of resources guidance documents which incorporate standards and the recognized standards themselves. Does that help?

CHAIR SHINE: So under certain circumstances, let's say the orthopedic situation, I

as an inventor or whatever would in fact know the standards I'm being held to, plus I would know what in fact obligations I would have to the agency with regard to the nature of the trials that I did, the results, the endpoints that would have to be measured, and so forth.

DR. KESSLER: It depends on the product, but yes. Dan?

DR. SCHULTZ: I think the answer is as Larry said, in some cases. The more mature the technology, the better the standards development and the better the guidance that we have. For cutting edge technology, and one of the reasons why we think it's important to have an active science group, is because there aren't necessarily standards that are developed. So we have to rely on the work of Larry's group and the work of other people who are looking at and studying these technologies to be able to make those assessments. The other thing about standards that should be understood is some of the standards are basically -- these are the tests that you should use

as opposed to these are the tests that you should use and the results that should be obtained. So some of the standards may say you have to do these tests, in which case we would still have to look at and see what the results were. Some of the standards are more specific, and require to meet certain standards, for lack of a better term. So, again, it's variable, but the goal is to try to get as many of those standards developed so that we can concentrate so that sort of the majority of devices can be reviewed using those abbreviated methods, and we can concentrate, for instance, on percutaneous heart valves, for which there are no standards, and things like that, where we need to put more of our resources.

CHAIR SHINE: The second question I have is can you give us an update on what's happening with the offshore development of devices, the concern that surfaced perhaps 50 years ago that manufacturers were going out of the country to do all of their trials, that the barriers were too great in this country. What's happened with the evaluations and the trials of

devices in the United States, and what do you see the trends developing in terms of the role of FDA.

DR. KESSLER: I have some answers, but I think that's really more a question for Dr. Schultz, talking about offshore stuff. Harmonization by doing.

DR. SCHULTZ: Yes, right. Well, that's why we've got Larry and all his scientists, because I don't do that stuff. You know, I think that it's an issue that is brought up, you know, not infrequently, that people are doing trials overseas. I don't think it's specific to devices. I think it occurs with all sorts of medical product. I think that it's not necessarily our issue per se in terms of why that's happening. I think part of it may have to do with the economics of clinical trials. I think in terms of the requirements that we put into place regarding clinical trials in this country, we do try to work with companies to try to make sure that the clinical trials are as least burdensome, streamlined, as possible. But I think the reality is that a significant number, especially of the early trials, the you know, so-

called Phase I, Phase II, although we don't necessarily call it that, are still done overseas. And I'm not sure we have a full answer to that at this point.

CHAIR SHINE: Dr. Laurencin?

DR. LAURENCIN: Two questions. What's the percentage in terms of your laboratory work, what's the percentage of work, research that's going towards development of new standards? For instance in that latex study, the work was for 10 years. Was that aimed toward just understanding, doing basic science work, publishing papers, or was that aimed toward new standards development? What's the breakdown in terms of your projects?

DR. KESSLER: I don't have an exact -- I'll give you sort of a rule of thumb. I think we spend probably around 20 - 25 percent of our time doing work that's fairly directed towards the standards world. I'd say another 20 percent of our time is basic mechanistic stuff. So early on in the latex work it was very basic mechanistic, trying to

understand how the molecules were adhering to the gloves, in other words, what is going on. How does latex and powder work together. So a lot of it was basic mechanistic. Eventually, toward the end of the latex, it was very directed toward developing a standard for how much latex and powder should be on a glove, or not on a glove, and how it transmits. And that sort of turned into a fairly directed regulatory question. We've tried to promulgate a rule, regulation, about gloves, based on that scientific work. So, you know, roughly 25 percent is standards directly. Another 25 percent basic mechanistic. Another 20 - 25 percent I would say is very direct regulatory stuff, and the rest of the time is spent doing consulting reviews, training, etcetera. Roughly.

CHAIR SHINE: Now, the draft guidance documents that are on the website. I mean, they may -- but their draft guidance documents, so they constantly change. How does that change, and maybe this is -- people already know about this, but how

does that change get noted? In other words, if there's a guidance document that came out in 2002 and a change has been made to it, how do you note that so that someone knows that the guidance document was recently changed?

DR. KESSLER: Unfortunately you just have to be a real avid reader of the Federal Register. That's the way we tell people. And there's no magic -- I don't know whether any website has an automatic update or a little flag. I'm not aware of that. I think the Federal Register is the way we do this.

CHAIR SHINE: But that's a criticism -- Can't the website say rewritten or re-drafted as of a certain date?

DR. KESSLER: It might. That's a good suggestion. I don't know whether it does. I'd have to -- if it doesn't do that, it's a great suggestion. Dan and I will take it back to the --

CHAIR SHINE: That's a major criticism in terms of by the device manufacturers is that the living documents, they don't know when it's been --

when it's had some CPR and it's breathing again for awhile, that a new regulation or something coming out of the laboratory that becomes a change in the guidance document in the middle of a study that they're working on may come about, and they have no way of being informed.

DR. KESSLER: Good point. The way we would then do that would be the Web. To try and do it otherwise would be hard. But putting it on the Web I think is a sensible thing. It might already be being done. It probably isn't. It's a good point.

CHAIR SHINE: Dr. Kessler, thank you.

DR. KESSLER: Thank you very much. Wait, one more thing. Do you mind, one second? We have just topped off the fourth floor of the Engineering and Physics Building. We're real proud of this. The new Engineering and Physics Building on White Oak is the next building under construction. And it'll be the next building after the shared use building it's occupying. We expect to be moving in around end of the winter, early spring, in a year and a half. So

it'll be '07. And I'd like to make sure that Norris and Jan, extend an invitation to each one of you to be at the opening ceremony to see it. It's about a $42 - $45 million building, and it's going to be a fabulous house for the engineering and physics work that's being done. And I would really like the Science Board to have a presence. Norris is grimacing because he's worried that all the congressmen and senators who will want to have face time will want to be there. It might be boring for you guys, but I really think it would be important to have the Science Board at the opening of the Engineering and Physics building. It will really be a dramatic place to research. I'm intensely proud of the effort. Designing it, myself and the whole office staff, and the architect, it's been really a labor of love, and one of tremendous minutiae, but it's been great, and I'd really like to invite you guys and hope you'll be there.

CHAIR SHINE: Well, thank you for the invitation. It appears that you also have an Oedipus complex, and you want us to join into it. We'll give

serious consideration to that.

Our last presentation as we mentioned earlier has to do with the peer review of the NARMS program. Is Linda here? Oh, there she is. Okay. This is entitled a peer review of the program, and Linda will describe how and in what way that review is undertaken. But again, I want the board to pay special attention to this because of the question of how and in what way we may want to follow up with regard to this particular review a la our earlier discussion. Linda Youngman is from the Center for Veterinary Medicine, and we look forward to her presentation. Linda?

DR. YOUNGMAN: Thank you very much. I'm here to represent CVM today. I'm delighted to represent CVM and to represent the program called NARMS, which stands for National Antimicrobial Resistance Monitoring System. And I just want to say, I did appreciate what I considered to be pretty supportive comments by the representative from Keep Antibiotics Working. We consider NARMS to be a really

strong program, and that's part of why we selected it for review, because we think even a strong program can be made better, and that's our aim in choosing it for review.

So 50 years ago, the war years, World War II, antibiotics were considered to be miracle drugs. They saved lives. And now what you see very often in headlines like this one is that antibiotics are no longer effective. And antimicrobial resistance is a growing problem worldwide, and there's a lot of argument. Is it caused from overuse of antibiotics in human medicine? Is it from veterinary medicine? We're not sure, but that's exactly why NARMS exists. We want to understand as fully as we can the real public health problem from antibiotic use in animals. We want to protect animals that are given antibiotics, and we want to protect the people that eat food from those animals. Next slide, please.

So NARMS stands for the National Antimicrobial Resistance Monitoring System. It is CVM's largest research program by far, and as I said,

we think it's a strong program. But even a good program can be made better. The aims are safer food supply, to protect public health, consumer confidence and international trade. Next slide, please.

So NARMS is collaborative nationwide surveillance of antimicrobial resistance, and it's conducted by CDC, who deal with the human arm of NARMS, FDA, who deal with the retail meat surveillance in NARMS, and USDA, who deal with animal isolates and slaughter plant samples. It's overseen and managed by the FDA, but it's very much a collaborative research program, and a very large program. Next slide, please.

The main objectives of NARMS are to enable risk-based decision-making. So we rely on data from NARMS in deciding whether to approve new antimicrobial drugs for food-producing animals. But we also use it to withdraw new antimicrobial drugs for food-producing animals. One recent example of that is the withdrawal of fluoroquinolones for use in poultry. So NARMS helps us with pre-approval, but it helps us with post-

approval also. It's a very important program.

NARMS also exists to help us promote prudent and judicious use of antimicrobials, to prolong the efficacy and life of antimicrobials so we can continue to use them by understanding where problems may occur and intervening. It helps us to identify emerging antimicrobial resistance problems. It helps us to guide prescription practices for antimicrobials in food-producing animals. It also helps us to encourage standardization of laboratory techniques. You heard a lot about that in Larry Kessler's talk. Standardization of laboratory methods is very critical to CVM also. We have a lot of our scientists who have been working on establishing NCCLS standardized methods. That's now CLSI. But standardizing the way that we characterize what's going on with antimicrobial resistance. And also to identify areas for more detailed investigation. Next slide, please.

I was going to call this NARMS: The Culprits. But these are the key bacteria that are

under surveillance. You've already heard a little bit about this, but in the U.S. salmonella and campylobacter are the most common food-borne bacterial pathogens. And those are those two up here at the top. Now, I got this quote from the CDC, and they say that there are about 76 million illnesses from food-borne -- food-borne illnesses from bacteria, viruses and parasites in the U.S. I've heard some people say 20 million. I heard somebody else say 1 million today. But I think this 76 million includes people who never go to a hospital, never go to a doctor. So I think that's more the correct ballpark. I've seen that many places. And only about 30 percent of those 76 million are thought to be caused by bacteria. The biggest culprit are viruses at about 67 percent.

In NARMS we're also looking at E. coli, which is this one here, and Enterococcus. And why are we doing those? Because they're not usually considered to be important food-borne pathogens. It's because they're commensals. That means they can carry resistance genes. So we're also surveying E. coli and

Enterococcus. But admittedly, most of our focus is on salmonella and Campylobacter. Okay, next slide.

So why do we want an external review of NARMS? Well, I started out by saying antimicrobial resistance is a growing public health concern worldwide. We want to use NARMS data to help us better understand that problem. We need national surveillance data to identify emerging problems from resistant pathogens. And this is a very complex issue. It's not simple. It's not as simple as you remove an antimicrobial and all of a sudden resistance goes away, because we've seen that that's not the case in some places. We need a system that permits early warning of impending resistance trends so that intervention measures can be implemented. So NARMS is an important program, and it has a lot of weighty issues around it, and that's why we want an external review of NARMS. We think it's a critical program for CVM. We're really proud of it already, but we're hoping to make it even stronger, and we hope that'll come out of this review. Next slide, please.

NARMS started for CDC in 1996. And in 1996, I don't have the map, but only about 25 percent of the U.S. population was represented. Today, the CDC part of NARMS includes the whole of the U.S., nationwide 50 states are represented and samples are collected, and in NARMS CDC they look at nine bacteria: campylobacter, Enterococcus, E. coli, 0157 E. coli, listeria, salmonella, shigella and vibrio. And so it's a comprehensive look at what's happening in the U.S. with human antimicrobial resistance. Next slide, please.

And these are a few of the important trends we've already observed. An increase in resistance to clinically important antimicrobial agents, and in particular fluoroquinolones, which I've already mentioned, which gave rise to fluoroquinolone-resistant campylobacter. And that's why CVM, on the basis of NARMS data, said we need to withdraw approval for the use of fluoroquinolones in poultry. That's why we need NARMS, to find out where there are problems, and to be able to intervene and do something

to take that problem away.

We're also keeping an eye of third generation cephalosporins in salmonella, and multi-drug resistance in salmonella. These are things that we're keeping an eye on, because if they do become a real problem we want to be able to do something about them. Next slide, please.

Now I'll switch to what FDA is doing. We are doing the surveys of retail meat. And I'm sorry, if you can push it one more time we can get the map in that picture. Thank you. As of November 2005 we have 10 FoodNet sites that are participating in the retail meat surveys. These are represented by the states in red. And we have public health laboratories that visit one grocery store per month, and they purchase 40 meats, 10 packages each of chicken, pork, turkey and beef. And all of those are cultured for salmonella and campylobacter. Those are the big culprits, the food-borne pathogens. Four of those 10 sites also culture for E. coli and Enterococcus. And we have introduced more representative sampling. As

of January 2005 instead of a convenience sampling where you went to a convenient grocery store, we now are going to randomly selected grocery stores to make it a more representative sampling. Next slide, please.

So the NARMS FDA portion, the retail meat surveillance, examines the prevalence of food-borne pathogens, and it also looks at the resistance to critical drugs that are important to veterinary and human medicine. And CVM's approach is really simple. We want to focus on the meats, the bacteria, and the drugs that are most important to public health, so we include beef, chicken, pork and turkey, and only those meats, only those four meats, and we focus on salmonella, campylobacter, E. coli, and Enterococcus. We do have limited funding, so we want to focus on the issues that are really important to public health. Next slide, please.

This is the animal overview for the USDA portion of NARMS. It's a directed sampling of the eastern U.S. only using HACCP program samples. HACCP

stands for Hazard Analysis and Critical Control Points. And in the NARMS USDA portion, isolates are collected from cattle, dairy cattle, swine, chicken, turkeys, cats, dogs, exotic species, and so forth. Isolates are collected from non-diagnostic sources, also animals that aren't ill, as well as diagnostic sources so animals that their samples go to veterinary clinics, and a small percentage of on-farm samples. And largely the samples are tested for salmonella and campy, E. coli and Enterococcus. Although there are a few other organisms that they look at when they're interesting. But this largely focuses on the eastern U.S., and it's using -- it's a directed sampling. It's not a representative sampling of HACCP control samples. Next slide, please. And if you can press it a couple of times again.

USDA -- sorry, this is sticking -- is focusing on the association between farm and slaughter plant. So they're sampling on farm, and I did say in the earlier slide that was a small percentage. But they're also sampling from slaughter plants. But what

they really want to do is understand what is the association between pathogens on the farm, from healthy animals on the farm before they go to slaughter, and what happens when the animals are slaughtered and there are bacteria that are shared among different species that are at the slaughter plant. So what is the association between farm and slaughter plant. Next slide, please.

In preparation for the review by the Science Board we did in late June of '05 our own initial review. We had a look at our programs, including the USDA and the CDC portions, and we focused on six specific aspects of NARMS. The first was the animal arm. I did mention it's not representative. We wanted to ask outside experts what was their advice on that. And the slaughter samples in USDA's animal arm are collected for salmonella only. So the question was is this adequate for other bacteria that we're looking at, that we're isolating and looking at resistance.

Also, we were concerned about the rinsates

for campylobacter. There were some questions that were raised because campylobacter dies so quickly, there were mobility concerns about that. So we wanted outside experts to look at what we're doing with that. We also introduced, as I mentioned earlier, the new random sampling for the retail meat arm.

We wanted to have the advice of outsiders to see if they thought could this be improved upon even more. Was the way we were doing the sampling, the new representative random sampling, correct, or should we go back to a different kind. How could we improve the sampling.

We also focused on data reporting. The annual reports that are published for the three arms of NARMS. We had people focusing on those annual reports to see if we could come up with a better way of reporting the resistance data and the prevalence data that we were getting from NARMS.

We also looked at the methods of molecular characterization. We also looked at NARMS international efforts, and asked were we focusing

appropriately on the international efforts. And we also addressed the future of NARMS funding. As you probably know, government budgets keep going down, and we have to deal with the money that we have. And we asked for suggestions for possible cuts. Which were the most informative parts of NARMS, which were the least informative. How could we get the biggest bang for our buck. So we did our own initial review already.

And the next slide shows some of the suggestions we've already gotten from external experts. One is that the animal arm sampling scheme could definitely be improved. And they said the sampling should be more representative. We should avoid multiple samples. We should probably try to avoid sick animals, and we should try to increase the proportion of samples that were coming from on-farm. It was thought that maybe the slaughter samples, there was cross-contamination, maybe they weren't as representative as the on-farm. And USDA wants to understand the association between on-farm prevalence

of pathogens and slaughter prevalence.

The sampling for the retail meat arm. There was a lot of support for the more representative sampling that we were doing, but they also thought we could do even better. For the pathogens that were less prevalent they thought we should do more focused sampling based on the data we were getting. Instead of sampling all the meats for a particular bug that seemed to be only in one or two types of meat, maybe just focus most of your sampling where you could get the biggest bang for the buck.

They also advised that annual data should be reported more quickly, and aim for a consolidated report. Right now we're doing a separate report for CDC, another separate report for USDA, and another separate report for the FDA. And the reports admittedly are coming kind of late, because once you get the samples for a particular year, then people have to do the laboratory workup, people have to do statistical checks, the data has to be entered, and you have to put it in the right format, and put the

right tables together, and there's a lot of lag between when the samples are collected and the data are reported. And so they wanted us to shorten that time, and also work toward making a consolidated report possible. So you could see are you getting resistance in animals, are you getting then in the retail meats, and are you getting the same kind of resistance trends in humans. And we could do that by putting all the information together.

They wanted us to review the molecular methods. They came back with strong support for the NARMS international efforts, which was great. And they also suggested that some of the less critical research activities, if we do have to cut, which we don't want to do because we think it's an important program, but if we have to re-focus and put more effort on the things that are really giving us good information, maybe we should consider doing that. So that's what came out of that initial review. Next slide, please.

So we've taken that information, that was

in late June of 2005, just a few months ago, and we're already working toward making the data available more quickly, getting the data in a format so we can put it on the Web so people can look at it and use it. And we're already working toward a consolidated report. As I mentioned, right now we have three different separate reports on the Web. If you look at CVM's home page, and you go to NARMS, you can get separate reporting for the CDC portion, the humans, the FDA portion, the retail meats, and the USDA portion, the animal origin isolates. So we want to have a consolidated report, and we're working toward that already. Next slide, please.

So what outcomes do we want to achieve from the external review of NARMS? One is, and I haven't mentioned it too much yet, but NARMS can meet the data needs for CVM for assessing new animal drug applications. You may know that CVM got user fees, and along with that come time frames by which new drugs have to be approved. And the hope is we can use NARMS data from drugs that are in a similar class to

help guide us towards, you know, safety considerations for new animal drugs that are coming to CVM.

CVM aims for excellence in the NARMS surveillance programs. We think it's a strong program, but even a good program can be made stronger, and that's what our aim is. NARMS annual reports are seen as more useful. We have been a bit criticized because the reports are from the three arms separately, and people have been saying do a consolidated report. So we're working toward that.

Also, another outcome is we want NARMS to be recognized as an early warning system, and position NARMS to help provide those early warnings if we can. What we really want, instead of just focusing on pieces, is to ask a broad perspective. We want to say what are the key elements necessary for critical public health surveillance of important food-borne pathogens, and does NARMS contain those elements. And if it doesn't, how can we change things? How can we restructure things to make sure it is the best public health surveillance system we can do for important

food-borne pathogens?

We also admittedly want to try to get some public recognition for NARMS for the really, the great program that it is, and have it recognized as high-priority public health surveillance, and a valuable national resource. That's what we're aiming toward, and we know we're aiming high. But that's where we're going with that. Next slide, please.

So this is our proposed time frame for review. And I appreciated having the opportunity to hear some of outcomes from the reviews of the other centers. Here we are in November of 2005. Even though we've done a little bit of work already, we're starting the review as far as the Science Board is concerned in November 2005. We've already put together names for an internal review committee. We plan to do a very serious and careful review of our own program by scientists who are working on NARMS and come up with some recommendations, a report that we could present to the Science Board. Then we're hoping in the spring of 2006, maybe summer, depending upon

the external review board members' availability, to have the external review happen, probably over two to three days, one time point only, and come up with some kind of a report from the external review board with the aim toward the final report being presented in the Science Board meeting in the spring of 2007. So this is a pretty aggressive time frame. We hope we can meet it. There may be some slippage depending upon very busy people's time frames, and how much time they have to devote to our review. But this is the time frame we're setting forth for ourselves. And we're going to start this month with our own internal review starting, so that we can have something ready for you by the spring of 2006.

I want to thank you for your time and attention today, and if I can answer any questions I'd be happy to.

CHAIR SHINE: Thank you very much. Questions, comments from the committee. Dr. Cassell?

DR. CASSELL: Yes. I commend you for wanting to have a review. I think it is a very good

idea, and I'm sure you appreciate that I think that the review, though, couldn't be done in isolation, and one would have to look closely again at what CDC is doing, and what USDA are doing, I believe. And I think the international perspective would also be extremely important, just for comparative purposes and lessons learned. And the other thought that I had is it seems to me, and this could be totally unreasonable, but given the very large amounts of antibiotics that we know are being used in aquaculture these days, in this country and other countries --

DR. YOUNGMAN: In aquaculture?

DR. CASSELL: Yes. In the consumption of shrimp in this country, and the number of different developing countries from which we actually import shrimp, I would just wonder how much do we know about food-borne diseases, bacterial diseases, that may be associated with some of these, you know, well with shrimp, but also possibly other fish and so forth, particularly since so much sushi is also being eaten these days in this country.

DR. YOUNGMAN: Sure.

DR. CASSELL: Just wonder about that. And then I guess with respect to the international scene, are there sister agencies in other countries that are accumulating similar data and have systems in place like NARMS that you could also get information from?

DR. YOUNGMAN: Okay. Well that's kind of three things, so I'll go through them one by one. The first is the review really is of NARMS as a program in toto. So we want a review not just of CVM's part, the FDA part of NARMS, but also what we're doing with the CDC portion and the USDA portion, similar to what we did in our own initial review. So we want to know are there ways we can improve all of NARMS, not just the FDA portion. So I take your point. We want to improve everything if we can.

The second part was about aquaculture. And I'm glad you asked that, actually, because even though aquaculture products are not one of the meats that we're focusing on in NARMS, we do have a very active aquaculture research facility at CVM, and we

have a fish veterinarian who's been focusing on doing a whole array of studies on the safety of different drugs in aquaculture-reared products. Now, CVM's facility focused on fish, but we're also working collaboratively with a group in CFSAN who have an aquaculture facility also, and they're doing a lot of work on shrimp. We're doing some collaborative research programs with the CFSAN scientists who were studying aquaculture-raised products. Admittedly, that is an important and growing concern because more and more of the fish that we're consuming in this country are from aquaculture rearing, particularly shrimp. So that's something we are working on, but it's not now part of NARMS.

The third question was about the international concerns, and you said something about are other countries doing similar types of studies like this. And the immediate answer is yes, there's a lot of countries that are doing this. Probably one of the most well known is DANMAP, which is in Denmark. And they've been doing very serious surveillance of

antimicrobial resistance in that country for some time, as well as looking at sale of antimicrobial drugs for different types of purposes, therapeutic, non-therapeutic, withdrawal of antimicrobial growth-promoters, that sort of thing. There are a lot of countries. There's CIPARS in Canada that's doing a very similar thing. And in fact, we interact with scientists from CIPARS and also from DANMAP in our planning for NARMS, and we want to continue to do more of that.

DR. CASSELL: I was actually thinking about Asia and South America in particular. In particular Asia, where you might try to get some of the same data since that's where most of the seafood, it's my understanding, is being -- is coming from.

DR. YOUNGMAN: That's true, a lot of the seafood is coming from Thailand and Asia and parts of Asia. We do --

DR. CASSELL: Bangladesh.

DR. YOUNGMAN: -- in our international efforts send scientists to China, different countries,

part of Global Salm-Surv, which is part of NARMS international efforts, where we try to interact with microbiologists around the world that are dealing with different problems, help in particular to introduce them to the type of techniques that we've been using, and also our standardization of methods. But we also collaborate with them kind of informally. It's not part of the NARMS structure, but it certainly is a very strong part of NARMS. And I think I mentioned, even in our initial review, it was one of the parts of NARMS that we got really strong voiced support for.

CHAIR SHINE: Other questions from the panel? A couple of things. First of all, let me share my ignorance. Why in trying to be more efficient was there a proposal to not test sick animals?

DR. YOUNGMAN: We do have funding constraints. One of the questions I was expecting was for somebody to ask what the budget is for NARMS. And I didn't want to answer that question because the answer is NARMS isn't just the budget for NARMS. We

spend a lot of money from other sources on NARMS. And admittedly, when our government dollars are going down, we have to look at things that might have to get cut if they're not as critical to answering important public health questions.

CHAIR SHINE: I'm asking the public health question. It's just not -- I mean, I would think that if you're at a farm and there were sick animals, that one would want to know what they were sick with. So I'm just trying to understand why in a budget-cutting environment you'd cut out the sick animals. This is my own naiveté.

DR. YOUNGMAN: Maybe if I can just back up and answer the question a different way then. There's nothing wrong with studying sick animals, and it's an important thing to do, if it helps you understand better what's going on in healthy animals also.

CHAIR SHINE: Yes.

DR. YOUNGMAN: If the healthy animals aren't necessarily coming down with the types of illnesses that you find from diagnostic samples from

sick animals, it's not helping you concentrate on what are the really important public health problems that you might get from antimicrobial resistance.

CHAIR SHINE: But how do you know that if you don't know what the organism is in the sick animal?

DR. YOUNGMAN: For -- maybe if I can say, if you over-sample sick animals only, it might make you think that Salmonella newport is a huge problem compared to other food-borne pathogens that are big problems too.

CHAIR SHINE: I'm not over-sampling anything. I just was curious about -- let me ask you to change the subject for a minute. We heard in the public testimony concerns about the USDA databases, and whether they in fact were being made available in an appropriate way for this effort. Do you have any comments about that concern?

DR. YOUNGMAN: Well, we have a very good collaboration with USDA and CDC. But I did say at the outset, even a strong program can be made better. And

we would like to work with USDA to make the sampling more representative. We think it would help us in informing us about problems in on-farm animal isolates.

CHAIR SHINE: So it is clear that in the course of this review, addressing such questions as the separate databases would be a relevant part of any review that we carry out over the next year and a half?

DR. YOUNGMAN: I think that the way we're reporting data is definitely something we want to focus on. I mentioned in our own initial review it was one of the things we highlighted that we wanted outside advice on.

CHAIR SHINE: Well, assuming that the commissioner wants to move forward with this, I think the board would be very interested in doing it. I happen to think that the time frame layout is actually a little generous, that we ought to try to do this a little bit more expeditiously than to have a final report in '07. But there may be constraints, and

we'll try to work with you and your colleagues to see if we can't do it in a very timely way. I think all of us agree this is a very high-priority area for health, and that we need to spend a lot of time and attention in doing it better.

Are there any last comments for -- Dr. Cassell?

DR. CASSELL: Sorry. I was just thinking that it seems to me also to be a very good time to maybe invite people that have not previously been focused on this area to serve on the external review, just to get maybe a fresh look and fresh ideas, and especially with a view towards maybe being able to take advantage of some of the newer technologies that have been developed in relationship to bioterrorism to see if they might not be a part. And I'm really thinking of biosensors. Maybe you're already doing this, and maybe you're already looking at that, but it might be worth considering.

DR. YOUNGMAN: Yes, thank you. We're not using biosensors in NARMS yet, although it is part of

the research that we're doing in CVM. But it's a part of another program.

CHAIR SHINE: Thank you very much.

DR. YOUNGMAN: Thank you.

CHAIR SHINE: In the last few minutes I think the board has an opportunity to have a conversation about anything that you've heard today, and the issues that you want to raise, any issues that you want to see addressed in the future, your reactions to, if you will, any of the presentations or any of the content that you've been involved in. Are there any observations? Dr. Harlander.

DR. HARLANDER: I guess I'd like to have a better understanding of this whole review process. Is this something that is -- just procedurally, is this something that is requested by various programs, or can the board make recommendations on programs that they would like to see reviewed, or how does it -- I guess I just don't understand how that works.

CHAIR SHINE: Maybe we could ask Norris to respond. I can respond to the last part of your

question with a direct answer, namely the commissioner has indicated that he will be receptive to our request to review anything we think ought to be reviewed. So I think at least with the current acting commissioner you have license to identify areas you think ought to be looked at. Please.

DR. ALDERSON: The easy answer to both of those, Dr. Harlander, is yes to both. The centers feel very strongly the value of peer review by the Science Board of any programs they feel they want to review. You've heard today of the one from CVM. You're probably going to hear another proposal at the spring meeting. So I think you're going to continue to hear this type of proposals to you in terms of where we would like your help in terms of looking at our science programs.

CHAIR SHINE: Dr. Thomas?

DR. THOMAS: Yes. When we began the pesticide review, it was obvious early on that there were other agencies involved in this, and that was just a moment ago reinforced with the players at the

USDA. And I think with the new commissioner encouraging partnerships, some consideration should be given up front to the composition of the committee. Now I realize that gets you outside the Science Board for the FDA, but it would seem to me that as a review process begins, and when there are stakeholders from the USDA and the EPA, they should be at least brought in to make a presentation to let whatever review committee know what they're doing.

CHAIR SHINE: I think that's an important observation. Let me recapitulate a little bit of what I heard, see whether you agree or don't agree. We have an acting commissioner. He's indicated that although he clearly doesn't know what his long-term tenure in this position is going to be, that he is in fact taking his tenure as acting commissioner very seriously and wants to move forward proactively. So I think the first conclusion I would reach is that the panel ought to take that very seriously and move expeditiously to building strong strategic programs between the Science Board and the commissioner. I

think I heard him say that that was something he was prepared to do.

In the course of the discussions today we've heard of several areas in which such strategic analysis might be useful. Information technology databases and the relationships of these is one priority area that a number of you raised. Some of us had the privilege yesterday of visiting with the Office of Testing and Research, and we were struck again by the notion that there were important projects going on there, for example, adverse drug reactions and so forth, where there was one database there, and then there are other databases around the agency which would be very relevant to those databases, but they had to be searched separately.

We heard a discussion about the difficulties of connectivity. All of those things are true, but those of us who are living in the electronic health record world are learning about connectivity, and various strategies to deal with that. But certainly IT and the areas related around it across

the agency was one of the areas that came up.

Another we heard repeatedly, and I think it was echoed by the commissioner, is indeed the role of science in the FDA, the support of science in the FDA. We heard presentations today in which an explicit approach to how you prioritize science was articulated. And I think given the size and scope of the agency that kind of prioritization is essential. At the same time, we also have heard over and over again that the resources for this have been very limited. And so a careful look at issues related to science and how it is practiced in the agency, what the shortcomings are, what the resource needs are, could be helpful in terms of not only providing an analysis, but also identifying what some of the resource requirements are that might be useful to the agency, assuming we can get the national debt to be moving in anywhere from a southerly direction.

A third area that we heard about was of course Critical Pathway. And I think the board has been enthusiastically supportive of the efforts in the

Critical Pathway, but we also believe there are portions of it that could benefit from careful scrutiny. That includes the application of science in the regulatory environment, how and in what way the regulatory process can be thought of as a quality improvement activity. And again, Dr. Woodcock has referred to this in a number of her presentations on the Critical Path. But the whole question of thinking about the regulatory apparatus, whether it's for devices, whether it's for biologics, whether it's for drugs, as a challenging continuous quality improvement, and perhaps taking a look at that from a little distance might very well be valuable.

I was struck in regard to the IT issue the number of times that we talked about the need for information, the pesticide need for more effective laboratory information to manage the system, the electronic data capture in trials. I mean, this is a pervasive issue, and it relates to also how we use science, and how we do the approval process.

We had a presentation on issues related to

post-approval surveillance, albeit there's some pre-approval activities. Clearly, the creation of the Safety Board was a response to principally post-surveillance issues. But we still have some real challenges with regard to what information is to be disseminated out of that activity, at what time, and what venues. There's reason to believe that some of that information produces anxiety among producers, manufacturers, so forth. And so they're going to be concerned at how soon you say what about potential risks. But balancing that against the public health's interest is going to be a challenge, and I think we may want to look more deeply into that issue in terms of what advice we might have as to how to find the right balance between the public interest, the professional interest in dissemination. And we had a discussion about some relevant activities there that we might want to undertake.

Janet Woodcock's presentation on oversight of clinical trials was a very important presentation because our whole enterprise in terms of both new drug

development, biologics, whatever, is at risk in an environment in which you have everything from problems with scientific integrity on the one end -- some of you have seen some of the articles in the last couple of weeks about retraction of articles and so forth -- to the notion of whether people are really being informed in an appropriate way when they give consent, to whether in fact we are overseeing trials in a meaningful way while they are going on, and the important responsibility FDA has with regard to the quality of those trials. And I think that information technology will be a critical role in that. I think we ought to think very hard about strategically how do we help FDA get the data it needs without in fact making the situation which is very complicated already more complicated.

And I think we've had an opportunity to see how an external review of one of the programs could be very useful, as I think it has been in the pesticide review. We now have a request from another review, but I think we're going to have to think much

more strategically about reviews. We can only do a certain number of them, and I don't think that we've had the opportunity yet to sit down, and Norris, this is something that I think I would like to engage you and the commissioner in, is how do we think about that review process. I mean, if you were going to look at this as a problem in health care, you'd want to do a risk assessment if you will. Where are the places where we're at greatest risk, where is the greatest leverage, where would a review make the most difference, and particularly under circumstances where resources are very limited, how do you make some of the hard choices as to whether you make those investments in Program A versus Program B. But the point is I think that, and this is, Dr. Harlander I think was right on target.

I think the issue is for us how do we go forward proactively with in-depth reviews, but do it in areas which are very strategic, where we have added value, and where we can be useful to the agency. It's my intention, and I think it was clearly articulated

by the commissioner, that we should move forward aggressively in several of these areas over the next several years, and hopefully if we're doing a useful job that can be helpful to everyone.

Finally, I think during the commissioner's talk it was Dr. Cassell who raised the issue of resources. And I would argue that resources for an agency such as FDA in the abstract is a losing proposition. You know, you can propose to double the NIH budget, and everybody who's got a disease will salute, and they'll help you double the NIH budget. Saluting to the notion that we're going to double the FDA budget as a general phenomenon is a non-starter. On the other hand, identifying areas where by our careful analysis we can demonstrate that resources would make a difference in terms of the agency's effectiveness in doing its job in protecting the health and getting new products to patients it seems to me is an area we can leverage. And I think we ought to, as we go forward Gail, as we examine these various areas, we ought to articulate where we think

limitations of resources is really impeding the agency's future, and its ability to contribute, and those kinds of arguments I think can be used in a variety of settings. You know, we've still got to pay for a war, a bunch of hurricanes, and God knows what else, a Medicare drug benefit, so if we start to work now, maybe we can make some progress in 24 months, or something of this sort. But this is a windmill I think we need to tilt with, and I think we can do that effectively.

So that's sort of a brief summary from my perspective of what I heard today. There may be other things that others of you identify that you want to put on our agenda, but I think it's a healthy agenda, and I think that pursuing some of these areas aggressively can be useful. And Norris, we're very appreciative of the personnel support we get. We know that you don't have lots of staff running around to help us do all these things. But we will try to focus ourselves on some of the key areas, and hope that we can get some staff support so we can provide some

added value, not just at these meetings but between meetings and at other times.

Any other comments by the panelists? Dr. Cassell.

DR. CASSELL: I certainly agree with what you've said, Ken, especially about the role of science, and would wonder especially about research and resources for research, particularly in the biologics and the vaccine area. And the reason I raise this is because of the dramatic changes that were made in those areas, you know, over the past five or it may be now approaching more than five years ago when they were cut so dramatically. The decision was made, you know, I believe to cut those programs. I'm just raising the question if it's time now to take a look to see how the programs are functioning without those kinds of -- the backup that they formerly had.

CHAIR SHINE: Thank you, Dr. Cassell. I would make just a couple of observations. First, the commissioner clearly has to get his feet on the ground, whatever metaphor you want to use to try to

understand his priorities and the issues within the agency. I think we would want to come forward with some fairly focused recommendations as to areas that would be strategic, and see whether we can move together. And I would pledge to the committee that I will be in touch with the commissioner over the next several months as he understands some of these priorities to try to -- that's one of the reasons I gave that little recitation of -- and we ought to add biologicals and drug research to that list. But I wanted to create a little, a series of agenda items we might talk with the commissioner about.

Second thing is that if you want to make the argument for resources, you can't do it on the basis of a one-hour presentation by a member of the staff which says we're doing a good job, but we could do a lot better job if you gave us more money. The way I think you have to do that is you have to in fact do a very careful analysis using some ad hoc reviewers, people who are highly respected in the field, who spend the time to analyze that issue, to

make a report to the committee, which if we want to endorse it can then become a vehicle for trying to address those issues. But it has to show evidence both of objectivity, that we're not simply arguing for an agency that we happen to have a connection to, but that based on some kind of data, and some kind of analysis by respected people in the field, that we've come to certain kinds of conclusions. So I would suggest today it's going to be a question of priorities, and I think we need to work with the commissioner on identifying those priorities, and secondly, setting up a methodology which allows us to do it in a way that's timely, but also that's likely to have some kind of impact as opposed to, you know, a self-serving request for more money, which is going nowhere.

DR. CASSELL: I hope you know me better than that to know that that's not. And I know very well we need hard data to get those resources. I'm just asking that we make it a priority to get the data.

CHAIR SHINE: Absolutely, Gail. You know, we've been at this long enough to know where we're coming from. All I'm -- I wanted to make a generalization, however, because I want people to understand that if we're going to make those kinds of requests, that's why we have to be able to look carefully at an area, with or without ad hoc reviewers, and come up with an analysis and a recommendation. It can't just be because this is the advisory board to the FDA, and we think the agency does good things, give us more money. That's my only point.

DR. THOMAS: Yes. The thrust of the external reviews has been to purposely avoid management issues, and certainly to avoid resource issues for the most part. So that will change the philosophy in how the review process proceeds. And there's nothing wrong with that, but that was just an observation based on my limited experience.

The other thing as it relates to reviews. I think it would be helpful for the continuity of the

Science Advisory Board to have, say, someone out of Norris's office put together a matrix for us, and those particular units within the agency that are subjected to review from time to time, and plug in the dates. We're going to have two people going off the committee now. Their historical remembrances of three or four years is going to be lost, so you know, each person coming on to the committee probably would do well with a matrix with regard to reviews.

CHAIR SHINE: I think that's right, and I also, you know, again, I'm sensitive to this issue of scientific review versus resources. I can't tell you the number of times that we put together studies with the Institute of Medicine and then we for a variety of reasons, including policy issues, tried to avoid the resource question. You would then make the presentation to the Congress, and the first question you got was what is it going to take in the way of resources. So you know, I think it depends on the charge, and the particular part of the organization we're dealing with. And I think what we want to do,

Norris, is formulate a charge for each review that looks at what in fact is the critical issue. And if one of the issues is that it's resource-starved, then clearly one has to take some kind of a look at that in the context of what it's able to do.

DR. ROSES: I have sort of a question about information more than anything else. The Institute of Medicine is doing a study on surveillance.

CHAIR SHINE: Yes.

DR. ROSES: What's the timing of that study? And should we be expected to align a review basically along with what is the best example, I guess, of an external?

CHAIR SHINE: Norris, do you know when that report is due? I mean, my -- Gail.

DR. CASSELL: The IOM council was told that it would at least take at a minimum probably a year. And I believe the committee really just started was it not in early summer. So they have a big workload.

CHAIR SHINE: Yes, I'm not anticipating a report from them before next fall. I mean, realistically I think we're talking September - October is my best guess, given the review process, and all the things that go on there. I would think that, (a), in addition to the agency getting that report, that report ought to be reviewed by this body. One of the things we discussed as you recall a year ago was that we were still going to play an active role in following what was happening within the agency on post-surveillance review at the same time that that study was going on. And I think the agency appropriately has been trying to move forward rather than to simply wait for that report.

I also think -- well, at the risk of sounding like I'm trying to drum up business for the Institute of Medicine, the FDA will be 100 when? Next year. I would argue that sometime, not during the time that they're doing the post-surveillance -- post-approval surveillance, but sometime in the next couple of years, I think there's room for some kind of a very

good sort of overview of the FDA's contributions and its future in a way that would address some of the questions that Gail was raising about people's perception of the agency, what it does, what it doesn't do. And there are so many misunderstandings of a whole range of issues, ranging from misunderstandings about what risk and what are tolerable risk levels, to how you make important decisions about benefit versus risk, etcetera, etcetera, that, you know, how shall I put it, the balance sheet at the FDA does not get a very fair reading, you know. How many good decisions balance on Vioxx exposé? Whether the exposé is accurate or not, the agency is constantly dealing -- those are the things that engage the press. And I think one of the questions that I will raise in another year or so is should we figure out some process. And the IOM -- in fact, it wouldn't just be the IOM, you'd ask the National Academy to do it because of the breadth of the FDA responsibility. But some kind of overview of the FDA's contribution to this country, as well as its

challenges, to put out for the public and policymakers. That doesn't mean that you're not going to have people how are going to still want to shoot at the agency. That goes with the territory. But I think frankly that the people who work in the agency deserve a better recognition of what they've done. And you know, I recognize that there's this concern about the agency being excessively cautious, or conservative about approval, and so forth. But the reality is there seems to be somebody around the corner ready to do something for everything that goes wrong, and not a hell of a lot of credit for everything that goes right. In fact, if I think back over the last decades, it was the fact that thalidomide wasn't approved which was the, you know, which was the thing which gave everybody a lot of attention to the FDA. Whereas in fact it deserved credit for a huge number of other kinds of things. So I think -- I don't know what the commissioner or the staff is planning with regard to the 100th, but I think somewhere around the 100th would be a good

opportunity to try to tell this story a little more effectively. Gail?

DR. CASSELL: I hadn't thought about this, Ken, but I really like your idea. And having recently participated in the NAS study on U.S. competitiveness in science and technology, which was at the request of Congress. The report was generated in record time. The request came in May, and we issued the report on October 12. And the advantage of that was that it was asked for by Congress, and it was a bipartisan request, and has received a lot of publicity, favorable publicity. And I'm wondering if that might not be a mechanism and something well worth thinking about on behalf of the board. Maybe we can talk about that later, but I think your suggestion is really an excellent one, and it certainly would be a way to ensure it would get a lot of attention if it were requested by Congress rather than by FDA itself.

CHAIR SHINE: Well, I've had similar thoughts, Gail. But I think before we did that I would want to get the sense of where the agency's

going, how it wants to proceed, and so forth, so that we're not undercutting them in any way. But anyway, these are some of the issues that I think.

Before we adjourn I would just like to emphasize to the board, first of all to thank Jennifer and Jim again. We appreciate your participation. But as far as other members of the board are concerned, if we're going to move forward with this kind of a strategic positioning, then we're going to need to be in touch before the next plenary meeting of this committee. As we develop our ideas with the commissioner, I'm going to be talking to some of you about areas that you have interest in where we could make a difference. So I hope you'll be open to the notion that this is not just one day and a half twice a year. This has got to be something that we are prepared some effort. And just as the work that John and Katherine -- I call her Katherine. Everybody else calls you Katie I guess. But you know, they put a lot of work into that report, and I think the result is, as others have testified to, have been very salutary.

So I think if we can use that as a model for how we make contributions, then I think that's a very useful thing.

DR. ALDERSON: Before we let people go, I want to follow up on Dr. Cassell's comments about the vaccine program. We are scheduled for the board to go to CBER in April. So if you've got specific things that you want to hear from CBER at that meeting, if you will get that to us we'll make sure you hear the questions you have on your mind. And Miles is here too, and so the timing is good to address the questions you're now bringing up. But we'll be glad to do that.

CHAIR SHINE: I would remind the committee that the commissioner has agreed that we can continue to have a little executive group to help plan meetings. So we will -- the staff will convene us in conference calls. That does not exclude other members from making suggestions about topics, but it's just getting a conference call with everybody on at the same time is a bit of a heroic event. But so we've

got four or five people representing different disciplines. I hope that you'll make suggestions, and that we would like to have some input, Norris, into how we can plan that meeting in a proactive way.

If there is -- Dr. Swanson.

DR. SWANSON: Just one thought on a potential topic for a future meeting. The acting commissioner mentioned pandemic flu coming up on the horizon. It is certainly a topic that crosses many of the different centers within the agency. And I think it might be very worthwhile to have an update, perhaps, at the next meeting as to the different activities that are progressing along that front.

CHAIR SHINE: I think that's a very good suggestion. Gail, I think -- or Norris can help you. I think actually we're $20 million in the President's proposal for FDA, which was essentially zero. You may --

DR. CASSELL: It may be -- but I haven't seen a breakdown.

DR. ALDERSON: What's being planned for

FDA is a supplemental.

CHAIR SHINE: It is. But it's still a relatively --

DR. ALDERSON: Very small number.

CHAIR SHINE: Yes.

DR. CASSELL: At least it's a dollar. I mean, that was what I was worried about.

DR. ALDERSON: It's in the supplemental that the staff have been working on this week.

DR. CASSELL: So it's not a done deal yet?

DR. ALDERSON: Oh no.

CHAIR SHINE: Yes, ma'am. Anything else? Let me thank all of the presenters. We had some good presentations. We actually got back on time without any difficulty. And I appreciate the work of the board. We are adjourned.

(Applause)

(Whereupon, the foregoing matter went off the record at 3:20 p.m.).