U.S. FOOD AND DRUG ADMINISTRATION

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SCIENCE BOARD ADVISORY COMMITTEE

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MEETING

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MONDAY,
DECEMBER 3, 2007

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The meeting convened at 8:00 a.m. at the Hilton Washington DC North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland, Kenneth I. Shine, M.D., Chair, presiding.

ADVISORY COMMITTEE MEMBERS PRESENT:

KENNETH I. SHINE, M.D., Chair
GAIL H. CASSELL, Ph.D., Member
SUSAN KAY HARLANDER, Ph.D., Member
LONNIE KING, D.V.M., M.P.A., Member
JOHN H. LINEHAN, Ph.D., Member
BARBARA J. McNEIL, M.D., Ph.D., Member
DAVID R. PARKINSON, M.D., Member
XAVIER PI-SUNYER, M.D., M.P.H., Member
ALLEN D. ROSES, M.D., Member
LARRY SASICH, Pharm.D., M.P.H., FASHP, Member
CATHERINE E. WOTEKI, Ph.D., R.D., Member

SUBCOMMITTEE ON SCIENCE AND TECHNOLOGY
MEMBERS PRESENT:

C. THOMAS CASKEY, M.D., FACP, The Brown Foundation, Institute of Molecular Medicine, and University of Texas Health Science Center at Houston

GARRET A. FITZGERALD, M.D., Professor of Medicine and Professor and Chair of Pharmacology, Department of Pharmacology, University of Pennsylvania School of Medicine (present via teleconference)

PETER BARTON HUTT, Covington & Burling and Former Chief Counsel, FDA

DALE NORDENBERG, M.D., Managing Director, Healthcare Industry Advisory, PriceWaterhouseCoopers

EVE SLATER, M.D., FACC, Senior Vice President, Worldwide Policy, Pfizer, Inc.

FDA PARTICIPANTS:

ANDREW VON ESCHENBACH, M.D., Commissioner of Food and Drugs

NORRIS E. ALDERSON, Ph.D., Associate Commissioner for Science

ROBERT BUCHANAN, Ph.D., Center for Food Safety and Applied Nutrition

JESSE GOODMAN, M.D., M.P.H., Director, Center for Biologics Evaluation and Research

LARRY KESSLER, SC.D., Director, Office of Science and Engineering Laboratories

CARLOS PENA, Ph.D., Committee Executive Secretary

CARL SCIACCHITANO, Office of Regulatory Affairs

WILLIAM SLIKKER, Ph.D., Director, NCTR

STEPHEN SUNDLOF, D.V.M., Ph.D., Director, Center for Veterinary Medicine

JANET WOODCOCK, M.D., Deputy Commissioner and Chief Medical Officer and Acting Director, Center for Drug Evaluation and Research

TABLE OF CONTENTS

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

(8:01 a.m.)

CHAIR SHINE: Good morning, ladies and gentlemen, and welcome to this meeting of the FDA Science Advisory Committee. We're delighted you're here.

We do have one member who we introduced briefly in absentia last time, but we're delighted that John Linehan is here. John is Consulting Professor of Bioengineering at Stanford. For a number of years he was Vice President of the Whitaker Foundation, giving away money, and is well known for his contributions to biomedical engineering as a field as well as in some of the areas of his specific interest. He is a member of the National Academy of Engineering, and we're delighted to have John as a member of the Committee.

The other new member is Cathy Woteki. Cathy is Director of Scientific Affairs for Mars, Incorporated. I'm waiting

to hear what the major advantages are of working for a candy company. But she has had a very distinguished career. She was Dean of Agriculture and Professor of Human Nutrition at Iowa State. Before that, she was the first Undersecretary for Food Safety at the United States Department of Agriculture.

She has a past which has included a couple of years in the Office of Science and Technology Policy. She ran the Food and Nutrition Board for the Institute of Medicine, and she is an elected member of the Institute of Medicine. So, Cathy, thank you very much. She will add a lot I think to our discussions in general, but particularly with regard to food and food safety.

I think the other members of the Committee are all present. I know -- happen to know that Gail Cassell is in town. I saw her at the hotel last night, so I anticipate she will be joining us shortly.

At this point, let's turn to -- oh,

pardon me, Carlos has a statement he needs to read.

DR. PENA: Thank you. Good morning to the members of the Science Board, members of the public, and to FDA staff. The following announcement addresses the issue of conflict of interest with respect to the meeting and is made part of the public record to preclude even the appearance of such at the meeting.

The Science Board will hear about and discuss the agency's Critical Path Program. The Science Board will hear about and discuss updates on the National Antimicrobial Resistance Monitoring System Program and activities related to melamine from the March 31, 2006, and June 14, 2007, Science Board meetings.

The Science Board will then hear about and discuss the Subcommittee review of the agency's science programs, and the Science Board will also hear about and discuss the

agency's updates on drug safety. Based on the submitted agenda for the meeting, and all financial interests reported by the Committee participants, it has been determined that all interest in the firms regulated by the Food and Drug Administration present no potential for an appearance of a conflict of interest at this meeting.

We would like to note that Dr. Larry Sasich is participating as the consumer representative, who is identified with the consumer interests. In the event that discussions involve any other products or firms not already on the agenda for which an FDA or government participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or

previous financial involvement with any firm whose product they may wish to comment upon.

We have one public -- open public comment period scheduled for approximately 4:15 p.m.

I would just remind all to turn on your microphones when you speak, so that the transcriber can pick up everything you state, and turn them off when you are not speaking.

I also request all meeting attendees to turn their cell phones and Blackberries to silent mode.

Thank you.

CHAIR SHINE: Thank you, Carlos.

With that, let's turn to our Commissioner.

DR. VON ESCHENBACH: Thank you, Mr. Chairman.

Good morning, ladies and gentlemen. Let me begin by adding my personal welcome to the new members, John Linehan and also Cathy Woteki. I apologize that I was, as often is

the case, on an airline last night and unable to get in in time for the dinner to personally spend some time with many of the Board members, but look forward over time to being able to have the opportunity to meet with you personally and share some of the vision for the future of this organization, and most importantly for the important contributions that you all make.

The Chairman has been very specific with regard to your unique talents and background and ability. They are, in fact, very important and crucial to the agency at this particular point in time.

And I want to add a personal note of thanks to Gail, who continues to serve, and I really very much appreciate her willingness, if you will, to re-up for another year of service to this extremely important board.

I come to you this morning and reflect on the fact that it has just been about one year since my confirmation as the

FDA Commissioner, and essentially two years since I first arrived on the scene as the Acting Commissioner coming over from FDA.

This past year, this past two years, have been times of enormous change within the Food and Drug Administration -- changes that have occurred by virtue of many external forces that have been impacting upon the agency, most specifically the things that have fostered a continuous increase in the scale and scope of the portfolio that FDA is responsible for.

And also, very importantly, changes that have occurred within the organization as we have been self-reflective and self-analytical and have addressed the question of what changes do we need to make in order to continuously be responsive to meeting our mission, to continuously protecting and promoting the public health in a context of a world that's radically and rapidly changing around us.

And your participation and your input as a board are extremely important components to helping us define, understand, and appreciate many of those issues, so that we can go about the process of determining, you know, what and how we must proceed.

One of the important points that has underscored all of that change is some of the things that regardless of change must always remain permanent. Those are, in fact, the values, the core values of the agency. And we have undergone over this past year or so a real assessment of those core values in a way that we will be able to continuously espouse those values in a way that they are both understood and appreciated by those we serve as well as become a living, constant guidepost for those of us within the agency in terms of carrying out our day-to-day business.

One of the important values that is reflected here this morning is the fact that FDA has always been, must always be, and will

always be a science-based regulatory agency. Its decisions must be based on what the science determines and dictates, what the data defines as the things that should be done.

And we have over the past year continued to affirm that and continued to find ways to be able to demonstrate that as we have carried out regulatory decisions.

But one of the other important pieces of the change process was to recognize not only the need to affirm that we are a science-based regulatory agency, but to appreciate the critical importance of science as we must also be a science-led regulatory agency.

Just as many other things in the world around us are radically and rapidly changing, so is science, and so are the tools and the technologies that science can bring to bear on very many critical and important issues.

We have gone about a process of

continuously assessing that role of where science can lead us in the future, as we have determined that as it relates to our own ability to do strategy planning, and to do that in the context of what research and development must occur within laboratories that we contain within the Food and Drug Administration, and do that in a way also to reflect what tools must be available in the field as we carry out analytical science and analytical assessment of the products that we're responsible for regulating.

There is much work that has been done. Some of that will be discussed later on this afternoon in terms of a report to this Committee, and then I look forward to that report being presented to the Food and Drug Administration following this Board's further actions and deliberations on that report.

But suffice it to say that we are continuously assessing the entire portfolio as it relates to our need to bring the tools of

modern science and modern technology into the regulatory process.

As we continue this effort, we look forward to our continued dialogue and our continued opportunity to benefit from your wisdom and your insight. As a board, an advisory board, like many other boards, you have an enormous opportunity to help illuminate that future in terms of the "what" that FDA must be addressing.

And I, as Commissioner, will continue to commit to you that I, the senior leadership of the agency, and the agency as a whole will continue to struggle, work, and endeavor to define the "how" we will carry out the "what" that is necessary and essential if we are going and will continue to meet our mission to protect and promote the public health.

I want to speak to you this morning about some of those opportunities and some of those initiatives in terms of how we are going

about continuously attempting to accomplish mission in the context of the rapid and radical changes that are occurring around us.

I alluded to earlier an effort at our continued strategic planning process. One of the most important aspects of that process has helped us to define a strategy for the future in which FDA, as it attempts to continuously achieve the high degree of success that it has always accomplished in the past in achieving its mission to protect and promote the public health, has now recognized that part of our opportunity and need to do that in the future will require us to be engaged in the total life cycle of the products that we are responsible for regulating -- engaged, if you will, right from the very beginning of production all the way through the process of consumption.

And that framework provides, if you will, guidance for the entire portfolio, because one could appreciate that whether

we're talking about food or whether we're talking about drugs or other medical products, being engaged in total life cycle from production to consumption enables us to help build quality in and assure the quality of those products even before they come before us for a regulatory decision to approve, disapprove, or allow to be approvable.

But at the same time, in addition to staying engaged in the front end of the process, in an effort to continuously improve the quality of the products that are being regulated, we must also stay engaged in the life cycle of the product even post-approval.

And so over the past year you have seen opportunities that have continuously been addressed with regard to our ability to enhance our efforts at post-market surveillance and engaging in products when they are being utilized in large, diverse populations, in which we have the opportunity to continuously learn, gain new knowledge,

modify, and continue to improve on our regulatory decision process.

Those kinds of efforts with regard to beginning to think strategically and beginning to think comprehensively, as an agency that is science-based, science-led, and is both proactive in an effort to be able to enhance the quality of products that are coming to the American people to assure, to protect, and to promote their health, is in fact at the core of what we must and always have done.

In an effort to carry out that mission, in that context of that new framework of reference with broad and extensive responsibility, there have been a number of initiatives which are already underway, initiatives that you've heard about on previous occasions, such as opportunities with regard to critical path, to bring new tools of science into that regulatory decision process.

And there have been new initiatives

that have been underway in an effort to continuously enhance our ability to partner and collaborate to expand our opportunities across that full life cycle of those products. All of that activity falls into a context of FDA having the capability to carry out that mission by virtue of two assets.

One asset is our authorizations, those things which Congress empowers us and enables us to do by virtue of legislative mandate and legislative authority. The second, in addition to what we are authorized to do, is our appropriations and the resources that are available with which we can then do it.

In that regard, I want to spend just a little bit of time talking about two areas or a couple of initiatives in both of those areas that I believe are important as it relates to FDA's future. With regard to authorizations, most recently a significant effort in that regard has come about by virtue

of the Food and Drug Administration Amendments Act, passed and signed by the President and now in the process of enactment.

That Act was a reauthorization primarily of our user fee programs -- PDUFA and MDUFMA -- but as many of you are well aware, it is in fact a very comprehensive Act that has over 200 initiatives which we are now legislatively empowered to begin to carry out, and it will enable us to significantly enhance and increase our ability to effectively respond to the challenges that are emerging around us as it relates to our regulatory responsibility.

That effort began a couple of years ago with extensive discussions, negotiations, and interactions, and carried through all the way through the legislative process. And I personally believe that at the end of that process FDA arrived at a place where this legislation will significantly improve and enhance our ability to be responsive to the

many challenges that are occurring around us.

Some things that occurred allowed for us to have authorization to increase the level of user fees for drugs and devices. This was an important part of the initiative, because in previous versions of those user fees, especially around PDUFA, we had recognized the importance of being able to have resources for pre-application consultations as a part of that strategy to build quality into these products at the outset by having the opportunity to work collaboratively with producers of those products to align them appropriately with the regulatory pathway.

One very simple example of the importance of this and the value of this occurred over the past year by virtue of CBER's efforts in terms of working proactively with vaccine developers along the lines of being able to implement good manufacturing processes that were science based, and in

doing so significantly enhanced the capability of vaccine production and the available of safe and appropriate vaccines to be available to the American people in an effort to be responsive to their needs and concerns, especially around seasonal influenza, and to set the stage for anticipated concerns that would arise in the event of a pandemic with regard to avian influenza. That proactive working at the very front end of the discovery and development process is in fact a formula for success.

Other new authorities will -- in that FD triple A, as it is currently being referred to, since "fa-dah" (phonetic) doesn't seem to be a particularly attractive way of describing that legislation, although I'm personally lobbying for FDA-cubed, since I think that sort of suggests expansive and exciting growth in that regard.

But one of the other things that is important is, as you look at this legislation,

will be the opportunities that provides for us having to do with post-market surveillance and our ability to create post-market infrastructures that will enable us to be able to gather significant information in the delivery and to the continuum, which will become a very important part and insight into further discovery.

We are actively engaged in a number of efforts, working to implement that post-market surveillance effort, but to do that again thoughtful and mindful of the critical role of science. Very soon you will be hearing about a major initiative described as Sentinel.

It builds on the efforts that have gone on already, in partnering with large clinical delivery systems, whether it's the Veterans Administration, the Department of Defense, and many others in which we will have access to data systems that will enable us to carry out important analyses of the impact of

these products when being used in large, diverse populations.

Most importantly in that effort, I call your attention to the fact that it is being done in the context of not simply having access to data and tools for data mining, from which we will generate enormous volumes of information, but most importantly to provide -- to apply to that a scientific discipline, to make certain that we are applying the rigors of scientific research even within that initiative itself, so that we can begin to understand the science of data mining as it relates to these critical parts and components of information, so that we can separate signal from noise, so that we can be absolutely able to affirm that the information that we are analyzing, and the knowledge that we derive from that, is accurate, precise, and true, and correct.

This requires not simply the acquisition of data and the recognition of

signal, but a scientific discipline of critical analysis. And that scientific body of knowledge will be developed and applied just as we are developing and creating the infrastructure.

I point these things out because this important legislation, as it empowers us to move forward, must also carry with it -- or we must carry with it the commitment, as we move forward, to do so in a thoughtful, careful, deliberative, scientific manner.

One other feature of the FDAAA legislation that I would like to call your attention to is that it also contained a provision for the creation of an FDA foundation, termed the Reagan-Udall Foundation. That foundation is a totally, completely independent 501(c)(3) foundation mandated by congressional statute, but separate and apart from the FDA in that it -- although it is charged by Congress to support FDA in its mission, it will have absolutely no

participation in any of the regulatory decisionmaking or processes or function that occur within FDA. And I wanted to share that very important aspect of the Board specifically with you as it relates to a complete understanding of the Board.

The Board has been constituted. Its 14 members have been appointed, and Mark McClellan, former FDA Commissioner and Administrator of CMS, now in the private sector, will serve as the Board's Chair. It is constituted, it is now in place, but pending outcomes of the continuous resolution it has not yet undertaken any function, nor has it been funded by any -- using any of FDA's resources.

Some of the important initiatives that this Board will undertake in an effort to support the activities of FDA's mission will be, for example, its ability to help create public-private partnerships that would be supportive of initiatives such as the one I

just recently mentioned -- Sentinel -- and also begin to address the important opportunity for support and creation of a very specific FDA credentialed fellowship program, which I have discussed with you previously in concept, as an important strategy to bring new, vigorous, intellectual capital into the organization in a very significant way at the level of individuals who are early in their career development and with a very broad and wide diversity of skills and new fields of disciplines in scientific expertise that will be relevant and important to the future of FDA's responsibilities.

That fellowship program has been underway with regard to its planning. It will ultimately, we anticipate, be able to bring into the agency 2,000 fellows. The program would extend over two years. That would allow a turnover of 1,000 fellows a year ultimately, and we would certainly look forward to being able to recruit from that fellowship class

approximately 20 percent of that group to stay in a long-term career path within FDA.

In addition to some of the efforts that are underway with regard to the new -- our foundation, I want to just simply remind you that a lot of effort spearheaded primarily by Janet Woodcock has already been underway in partnerships and collaborations with the foundation for NIH, and also activities such as the C-Path Institute, which are continuously efforts to improve the ability to bring into the agency assets, partnerships, collaborations, that leverage and expand our ability to meet mission.

In addition to some of the efforts that have occurred within FDAAA, many of you have had the opportunity to see the food protection plan that FDA has recently released and is currently under consideration, both by the administration, and ultimately we anticipate by Congress, in which there are additional authorizations that are being

requested in an effort for FDA to carry out some of its specific responsibilities with regard to enhanced ability to protect our food supply, whether imported or domestic, and from farm to fork, or production, if you will, to consumption. So we look forward to a variety of efforts that will enable us to expand our impact.

The appropriations that are necessary for these activities have also continuously been an important focus for the agency, but to do so in the context of creating an adequate business plan that matches the strategic plan, to be able to define specific initiatives that would justify and, in fact, compel an appropriate investment on the part of the American people by virtue of appropriations, by being able to provide value added to particular stakeholders, like industry, such that an increase in user fees for very specific, very unique, and particular deliverables would also be an important part

of that resource base.

And as I've just alluded to, we now have an opportunity with regard to our own foundation for certain appropriate activities to be supported through that process. And so we look forward to continuing to build the resource base of the institution to support its programs.

And specifically with regard to the budget, beginning two years ago when I arrived, we began a process of attempting to significantly increase the appropriations coming to FDA over a period of time as part of an expanding increasing investment in FDA's portfolio.

In 2007, increases were recognized and we -- as we have moved into 2008, the budget that is currently under consideration has in fact significant increases associated with it, but the problem that we are currently faced with is that we are in the midst of a continuing resolution.

And so although the budget itself, as presented by the President and as considered by Congress, has increases in both appropriations and increases as it relates to our user fees, we are continuing to function at a level comparable to '07, because those -- that budget increase has not yet been passed into law.

We would hope that the continuing resolution that is expected to expire later this month will result in an actual passage of the bill, but that continuing resolution may continue into the next calendar year. That is something yet to be determined by Congress, but it does present significant concerns for us.

We will continue to work with all of our partners in developing and presenting a cohesive, coordinated, and compelling resource request package, especially to the administration and to Congress. And we are currently in process of working with OMB on

the development of our '09 presentation, and that hopefully will be finalized over the next few months.

In addition to the need for our addressing authorizations and appropriations, a few other particular points that I'd like to share with the Board as it relates to FDA's continued ongoing effort at addressing its mission has been to recognize the extraordinarily important role that globalization pays.

This was no more apparent perhaps than very recently in FDA's prominent role in the President's Import Safety Initiative, in which when one looks at the safety of imports coming from other parts of the world, and the rapidly, radically increasing volume of those imports, a large portion of that portfolio is made up of products that FDA regulates, including obviously food and drugs.

And so we have been actively engaged in that Import Safety Initiative.

That's a very global one involving many of the cabinet secretaries and departments within the government, and we have been specifically focusing on food and doing that in a way of expanding FDA's presence beyond its borders, again along the concept of being engaged in total life cycle and being able to build quality in by working with production outside of our borders, specifically working with countries in which infrastructure is not as mature as it is in other parts of the world, and by being able to create increasing capacity.

I regret that I cannot spend the entire day with you, because I leave this afternoon to attend a meeting in Dublin, which will be the Second Summit of International Regulators, my peers if you will around the world.

You may recall that last year, as part of FDA's centennial, recognizing that actually those drug regulators had never ever

met together at one time. We took the initiative at FDA to host the first summit; 24 regulators from around the world did in fact come. All 24 will once again be present in Dublin.

Our focus is on looking at opportunities, particularly around drug regulation in the new molecular era to find ways for further harmonization. And we will specifically be addressing the problem of counterfeit drugs on this particular meeting in Dublin. And, obviously, all major countries and sectors are represented.

I return on -- from that meeting on Friday of this week, and then leave Saturday for Beijing, at which point I will be participating with Secretary Leavitt in finalizing memoranda of agreement with China as it relates to our ability to address increasing capacity.

Those two memoranda are one with the Chinese State Food and Drug Administration

in which the relationship between U.S. and China around drugs, especially active pharmaceutical ingredients and excipients, and many other important components of drug production coming from outside our borders is an important issue. And also, with their AQSIQ or their export certification agency, specifically around issues having to do with food.

And so those hopefully will be very productive as well as very satisfactory, ongoing interactions with someone who has continuously emerged as a very important major player with regard to the products that are coming into this country that FDA is responsible for.

So the international effort will continue, as well as our efforts as it relates to continuously collaborating with other partners.

There is no question that this is an agency that when I arrived two years ago I

found to be stressed, stressed by virtue -- and I also said stressed and stretched -- stressed and stretched by virtue of the radical changes that are occurring around us as it relates to science and technology and the impact that that has on the nature of the products that we are responsible for regulating.

Changes that -- stressed and stretched by the radical changes that were occurring in how those products are derived, many of them no longer being domestically produced but coming from countries abroad, and no such thing as made in U.S.A. or China or in Europe, but rather assembled in those countries, and probably no more an important example of that than the way medical devices are currently being assembled.

And continuously stressed and stretched by the fact that the response or the expectations of FDA's performance continue to be centered around the fact we are and are

always looked to be providing the leadership as the world's gold standard. FDA will not, has not failed in that responsibility. It still is and remains the world's finest regulatory agency, able to continuously assure the American people that it is protecting and promoting their well being and their health.

But those of you in this room and I recognize that as successful as we have been yesterday, and are today, that if we continue to simply be the way we were yesterday and today we will not be successful tomorrow. Change must and is occurring, and change is occurring within this agency.

And we will continue to work collaboratively and cooperatively with you to define the "what" that the future holds in store for us, and hope that you will trust us to be thoughtful and creative in terms of how we will go about the process of being responsive to that new opportunity.

I'm going to stop here, use the few

more minutes of my remaining time for some questions from the Board, and then I do want to take a couple moments for a special presentation that I'd like to make.

But I'll -- Mr. Chairman?

CHAIR SHINE: Commissioner, thank you for your comments. I've had the privilege of serving on the Science Advisory Board under three Commissioners. And since I'm not ranked for high office, nor have any desire to continue on advisory committees, I feel free to make some observations to you, Mr. Commissioner.

First, to recognize the courage and wisdom with which you brought to this Board a year ago, a request for an examination of the science programs within the FDA. That was wise, because it took advantage of the scientific expertise on the Board, and three members of the Board served on a Subcommittee.

It also brought some 30 scientists from the academic community, from industry,

from a variety of other backgrounds, to look at the science situation and opportunities within the agency; encouraged because whenever you ask anyone to take a look at your programs they are in fact going to be looking for suggestions, critique observations, and that takes a significant amount of both self-confidence and courage, and I commend you on that.

I want to emphasize -- and you won't be here for the discussion this afternoon -- but as I have read the report from the Subcommittee, it is clear to me that one of the principal concerns of this group who are really very much supporters of the FDA, as is this Board, we care about the agency, we care about its future.

One of the principal concerns expressed there was not in the management of the organization per se, although there were some suggestions, but with regard in fact to the resources.

And we recognize that in your role as Commissioner you are part of a process which has to address resources in an orderly manner within the administration, but I think it is clear that for those of us, particularly for someone going off the Advisory Committee, that the necessity for finding more resources and not just from fees but from appropriations is an important challenge and one which many of us outside of the agency and outside of the government have a responsibility to do in order to help you deal with a stressed and stretched organization.

I would also like to request that you communicate to the staff of the FDA on behalf of the Science Board that we have had the privilege each year of evaluating nominations for awards for scientific contributions. And we have been repeatedly impressed with the quality of those contributions.

It has been in many cases very

difficult to make a choice between two finalists, given the quality of the science, that the critique which we are going to discuss this afternoon represents the sense of our Subcommittee and these consultants that we must do better, that we have areas that we can strengthen, but that this in no way minimizes the sense that this Board has of the dedication and skill of many, many members of this staff.

And I believe that nothing we conclude in the course of the report should in any minimize those contributions, recognizing that the environment in which they work and their future depends upon a variety of changes including substantial increases in resources that will allow the agency to go forward.

This Board strongly believes and supports your motion that this is a science-based organization. Not that it does all of the science itself, but that it works closely with other agencies, but that there are

certain kinds of science that it must do in the area of regulation, science that others will not do because it relates to how and in what way the mission of the agency is carried out.

And as we debate these issues this afternoon, Mr. Commissioner, I want to emphasize that that debate occurred because you asked for it. And I commend you for that, and I want to extend my appreciation to you for the notion that you have suggested that you will continue to use the Scientific Advisory Board, sometimes painfully, but I think always constructively, in support of this agency. And I want to thank you for that support.

DR. VON ESCHENBACH: Thank you, Mr. Chairman. Just let me, if I may, take a second to respond. I will look forward to the report from the Science Advisory Board after you've had an opportunity to appropriately deliberate on the report that is being

presented to you this afternoon by the Subcommittee, along with many important advisors.

I recognize full well the tremendous effort that went into this over this past year as people have worked exceedingly hard to be thoughtful, insightful, and to grapple with many of the issues and many of the challenges. And in response to that, I want to assure you, Mr. Chairman, and the entire Board, and hope you will communicate that to the Subcommittee, that that report will be given our serious and full consideration and deliberation, and will be utilized as effectively as we can in the context of shaping, defining, and implementing the most appropriate scientific portfolio for this agency.

I appreciate the point that you made that the -- and why it was so important that we do this. It is precisely because of the fact even if we had all -- an unlimited

amount of resources, it would be in appropriate for FDA to consider or think that it would or should do all the science that was necessary to be a science-based, science-led agency, but that it must be certain it is doing what is essential and appropriate within the agency, both as it relates to developing the tools that will enable us to make scientific decisions, as well as what we must be deploying in the field as it relates to our ability to analyze products and make regulatory assessments.

But at the same time, to do that in the context of the radically changing world around us where science is emerging in multiple places -- NIH, in industry, in academia -- and how we can find our appropriate part and place in that larger collaborative effort, so that FDA benefits from and does not in fact function apart from or in a vacuum is a critically important challenge.

I believe that we are at a crossroads where there is a larger societal question that is before us. And it's not a question to be answered solely by the FDA, but I believe we are in the process of attempting to provide all of the information upon which that question can be based, and that is: what do we as a society wish the FDA to be? And what capacities and capabilities will it and should it have as we go forward in the future?

That's a question that I think is larger than the one we're addressing right now, but it's the context in which that question has to be addressed. So we are in the process of working with you. We'll continue to work with you, and I want to assure you the seriousness of that on FDA's part.

CHAIR SHINE: Thank you.

Questions for the Commissioner from the Board?

DR. VON ESCHENBACH: Cathy, did you

-- oh.

DR. WOTEKI: Yes, Commissioner, thank you very much for your remarks and setting the context for us. I was particularly impressed by your discussion of the necessity of engagement in the life cycle of products across the whole portfolio that fall under FDA's regulation.

And I was just wondering in the context of the remark that -- and the conversation and interchange you've just had of what the implications are for FDA for the future of moving into a life cycle approach towards regulation of these products.

DR. VON ESCHENBACH: Well, there are two important implications I think. One simply reflects something that I think has been an important discussion over the past two years, and that is the recognition that if we are going to be engaged in total life cycle what essentially FDA is is an information management business.

It acquires data, it assembles it, analyzes it, assimilates it into a context, acts, and then continues to acquire more data after that action. One of the implications is creating the information technologies and the bio-informatics, if you will, infrastructures that must in fact underpin that new full dimension portfolio.

So we have been working on IT infrastructure. We have been also working on the informatics that are going to be necessary with which to gather the right data and be able to be certain that we're analyzing that, carrying it through that process, so, as someone said, data goes to information, information goes to knowledge, and then in fact truly knowledge goes to wisdom. And that should be the framework of that regulatory decision. So one implication is: do we have the right tools with which to do that?

Secondly, the second implication is we cannot do that simply within the walls of

the FDA. We must be working outside of our own, if you will, borders. And that requires greater interactions, collaborations, and many of the things that you see us embarking upon, whether I talk about relationships with regulators in other countries, whether it's greater dialogue and interaction with regard to the developers by virtue of things that have occurred, and the new FDAAA legislation with resources for pre-application consultations, whether it's working with our sister agencies like NIH, CDC, CMS, etcetera, all those are intended to allow us to be able to participate across that full continuum and be constantly engaged with the product in a way that we can learn, understand, and make regulatory decisions when necessary and appropriate.

CHAIR SHINE: Any other questions?

(No response.)

If not, I guess we can proceed.

DR. VON ESCHENBACH: Well, I have

one of those bittersweet responsibilities at this point, but I see it more as a great opportunity than a responsibility, and that is to both pay tribute and to say thank you to individuals who have served this Board so well and have given so much time, effort, energy, and mostly have given their passion and their commitment to the cause.

This is an agency I have found that when one asks what's the secret of its success, it's in the people who make up the agency, and it's not only the people who are inside the agency working on a day-to-day basis in Rockville or White Oak or any other part or place of the -- it's also the people who have made their life, their commitment, a part of the agency as well. And certainly the members of this Board exemplify that so well.

And so I want to take a few moments and present to individuals who are leaving having served so well, and the first is to Susan Kay Harlander. Susan, you've brought an

extraordinary dimension to this Board. Obviously, food is the first part of the Food and Drug Administration, and I have to tell you that although there are some who are wondering whether it should continue to be so, I personally think the vision and the insights that you have brought really help continue to crystalize the fact that as one thinks about health and protecting and promoting health, there probably is no other single thing we do or put in our mouth every day that is responsible for preserving and maintaining and nurturing our health than the food we eat.

Food will and always will be a critically important part of mission, and you have been a critically important part of helping us understand the importance of that mission. And I want to thank you for your service.

MS. HARLANDER: Thank you.

DR. VON ESCHENBACH: Xavier Pi-Sunyer, where is he? We talked just a little

bit a second ago about food and the importance of food in the Food and Drug Administration and health, and probably one of the most critical areas in public health that we're facing is the problem of obesity and the problem of malnutrition if you will.

And one of the important parts of FDA's vision for the future is to see its role as helping people to understand how to use the products that we regulate, and part of that will be our continued effort, whether it's in the food label, modifying the food label, or in many other initiatives, to help us continue to address the problem of obesity, and most importantly to look at it also from the point of view of the consequences of diabetes as that -- as becoming an important part of it, and what we must be doing to deal with diseases that result from problems having to do with nutrition.

Your wisdom, your insight, your guidance in the science that must underpin

that have been important contributions --

MR. PI-SUNYER: Thank you very much.

DR. VON ESCHENBACH: -- and we're so grateful to you.

MR. PI-SUNYER: Thank you.

DR. VON ESCHENBACH: Allen Roses. I talked earlier about FDA being a science-based and a science-led regulatory agency. And Allen has brought that cutting edge vision and fields like pharmacogenomics where many, many are still grappling and struggling with where these new cutting edge scientific fields must and need to fit into the regulatory pathway and the regulatory process, and our ability to understand getting the right drug to the right person for the right reason, based not only on parameters of their disease but based on the parameters of what they are as being made up by their genes as a human being and as a human person.

And, Allen, helping to define what

those cutting edge new areas of science are that we must be utilizing to illuminate has been an extraordinary contribution and one for which FDA will continuously be grateful.

Thank you very much.

This next presentation is a year old. When I first arrived -- actually, it's more than a year old. When I first arrived at FDA -- and I truly meant what I said all along, how critically important this Board is to the FDA and to its mission and to its role -- and recognizing that because of that I wanted so much to be able to work with the Board, empower the Board, to be able to reflect that critical leadership in helping us to illuminate the future.

One of the things that was so special to me was that I had the privilege of already being aware of the tremendous leadership capabilities of Ken Shine. I was well aware of his enormous contributions to science and to academic and to education, and

to his ability to bring people together from a variety of diverse backgrounds and help them focus through the prism of science on what could and needed to be done to change the world.

And to be able to do that in terms of what could and needed to be done to continue to help FDA address the changes it had to make was probably one of the most important gifts or assets that I could have hoped for as a newly arrived Commissioner.

There was one problem. The problem was his term was over on the Board, and he no longer needed to continue to serve. But by virtue of the fact that the need was great, Ken did what Ken always does, and that was serve even more and serve beyond -- over and above the call of duty. And so he agreed to extend his leadership as Chairman of the Board and to continue his participation on the Board.

I will have to tell Ken -- I'll

confess publicly -- that although he signed a contract to do that for one year, I was working behind the scenes with Norris to see if I could be able to work to renegotiate an even further contract extension.

And, Ken, the only thing that has kept me from actually doing that and speaking to you was Norris came back and said it was absolutely, unequivocally, irrevocably illegal for me to do that. And so I've always promised that I'll do anything I can for FDA except anything that is illegal or immoral.

And since it was illegal for me to ask you to serve any longer, I am, therefore, taking the opportunity to present to you this plaque that is just a very small token of not just the appreciation but the affection that everyone at FDA has for you.

This is an agency made up of individuals that I believe exemplify the word "public servant." You, sir, are a public servant par excellence extraordinaire, and

your service to FDA could never ever be reflected simply in a plaque. But it will be reflected in the spirit of this agency and the people who serve it and the people who will continue to serve it now that your term as Chair has appropriately come, and legally come, to an end.

(Applause.)

CHAIR SHINE: Thank you very much, Commissioner. It is always good to know that we are within the law.

(Laughter.)

With that, we're going to go to our agenda. One of the individuals who is in that other staff who has been just an extraordinary leader during my tenure here has been Janet Woodcock, who is Deputy Commissioner, and she is going to give us an update on the critical path.

Janet?

DR. WOODCOCK: Thank you, and good morning.

Carlos, I have about, you know, 45 minutes, so I'll try to keep it short, or I can -- you can cut me off or tell me when to accelerate. I don't mean to take up a whole lot of time.

Let me figure this out. Where do I point it? There we go.

All right. I'm going to give you an update on FDA's critical path initiative, which is something that has been going on for a number of years and is beginning to bear fruit and is intimately related to many of the scientific topics that will be discussed this afternoon by the report of the Subcommittee. So I will try to relate some of what I'm saying this morning to what the Subcommittee has to say in their report.

First, I'm going to give a very brief introduction, a conceptual framework, what is critical path. I think people continue to be a little bit confused about that. What we've accomplished so far, some of

the assessments and what the critics are -- you know, various critics are saying about critical path, where we want to focus in 2008 and longer term, and then perhaps get your input on that.

So the conceptual framework -- when this first came out in 2004 was a time when drug and medical device discovery and development, the pipeline was not very robust, and that issue continues to this day. Where in the '90s there was a very robust flow of products, that has diminished, particularly in the pharmaceutical area.

And multiple explanations of this problem have been offered by various experts, but critical path offered a new explanation, which was that there had been a lack of investment in the science that actually supports the development of the products.

And although we framed this in terms of the pipeline problem, this had been an issue for FDA for a very long time, because

the science that FDA does, and much of which you'll hear about this afternoon, relates to the applied science of development and evaluation, how you actually evaluate these products as they are being developed and then as they are perhaps -- before the agency -- for marketing and then looking at their performance out in the market subsequently.

And FDA scientists had been working on these issues for a very long time. We called it regulatory science, and that was such a non-starter in terms of the world. People did not want to hear about regulatory science, that applied science, so now we -- now this was impacting actually the development of the products themselves, we felt, whereas before it had been more of a problem for the FDA in evaluating the products.

And so because this was now a mutual problem, we felt it would get more traction, but we renamed it and

reconceptualized it and called it critical path.

And for -- we initially started out with critical path simply for the medical products, and we have this diagram -- and I'm not going to go over this in great detail, but basically the message was that the discovery science, basic scientific research, biomedical research, is different than the science that is used to develop and evaluate products once their scientific discovery is made.

And critical path we consider as a bridge between discovery and delivery, but -- and it's a different science -- this critical path research that needs to support that bridge is a different set of sciences. And, of course, you're going to hear all about them this afternoon in the report from the Subcommittee. These are the sciences that actually support moving a product down and evaluating a product.

And actually you'll hear later in

this talk that now we have moved critical path further down. As the Commissioner said, in the life cycle approach we used many of the same evaluative techniques to look at the performance of the product once it's out on the market during a further stage in the life cycle.

So what we tried to do -- and I think our first actual achievement of the critical path initiative -- was actually defining this problem. As I said, we had never really gotten very much traction when we talked about regulatory science, that members of the Science Board I think understand this, but the broad community stakeholders did not, and that includes Congress, the medical community, and so forth.

Many people felt that FDA, in doing its evaluation, was basically doing a regulatory enforcement action. We simply would make an action and would not understand that there had -- there was a vast amount of

science that had to go into this decisionmaking. Otherwise, the decisionmaking would simply be arbitrary and capricious.

The problem was no one really owned this science, although FDA scientists and reviewers were uniquely positioned to understand the gaps in this science. As a result of this, we were often blamed for development problems. Okay?

Something goes wrong during development, something goes wrong after a product is out on the market, or we collectively fail to detect a problem with a product that's out in use, and people think, well, that's something -- you know, something has gone wrong. But often, as you know, the actual case was there wasn't the applied science available to support the proper evaluation or proper regulatory steps.

And this is very important, this second bullet here, and I think it really relates to what will be talked about this

afternoon. Because our stakeholders have never conceptualized FDA as needing to do this, they really have not had a very clear idea of what regulatory science is, the agency was generally not resourced to support the applied science necessary to modernize our regulations and modernize development. In other words, we didn't have the scientific resources to do this.

And as you have already heard from Ken, and from the Commissioner, our scientists to this day make heroic efforts to bridge these scientific gaps, by collaboration, by their personal efforts, and so forth.

Now, the biologics and device programs do have very modest research funding, historically. The foods program has had fairly modest research funding, but the drugs program has really never had any significant research funding, scientific funding. And you may hear about this this afternoon a bit.

So what we tried to do is

communicate -- and this is, again, the early part of the critical path initiative -- reach some kind of agreement on addressing the problems. The stakeholders, such as patient advocacy groups, really understood critical path faster than any other group.

And this is quite interesting, and we think -- I think the reason is they had long been investing in research, and the patient groups were extremely frustrated at the progress of that science through the development process and realized that there were still major gaps preventing that advance -- those advanced scientific discoveries from progressing into development.

The industrial sector agreed with the problem definition, but they weren't really sure whether they should play. FDA staff, because they had been doing this forever, I think were skeptical that this would bring more help to them. That's really what they need. They certainly -- all the FDA

scientific and review staff agree on the need for research and support of their regulatory science, but they were unsure that critical path would actually be able to help them.

This has changed, as I'm going to talk about later, and we have a very enthusiastic group of people who would really have a tremendous number of scientific projects that need to be done. So it's clear this is a long-term effort.

So what did we do, given that critical path itself didn't bring any new resources? We emphasized collaborating ways of accomplishing the objectives. It's clear that the basic science community, as well as the industry, as well as patient and biomedical community, have a stake in getting these products made available, and also having them be well evaluated.

And, therefore, we all have a stake in sort of getting this done in the common ground, so perhaps we could come together in

collaborations and make this happen.

Another objective is to pool existing resources, because funds were scarce. One of the issues that had arisen is that the -- many of the industrial development programs -- and this is true in devices, pharmaceuticals, biologics, and it's also true to some extent in the foods area and others -- that the industrial sector had kept much of the information they had generated confidential, and so it wasn't being shared.

And so there's huge amounts of information -- clinical trial data, animal data, and so forth -- that wasn't -- didn't move to knowledge, because it was not shared. So we -- part of the goal of critical path was to pool this information and use it, and also to use NIH-funded trials not to simply answer a single question of the researchers at NIH but also to accomplish some of these broader objectives, and we are doing that.

So we identified in critical path a

number of areas that were critical for improvement, including biomarker development clinical trial modernization, bioinformatics, and manufacturing of products, and I'm going to go through some of these briefly and talk about the progress.

And these are the areas I'm going to talk about for biomarker development. In biomarker development, I think our first area of progress has been to get broad acceptance of the notion of qualification of a biomarker of fitness for use. Up to this point, everyone talked about validation of biomarkers, and primarily talked about surrogate endpoints, which are endpoints that can be -- that are biomarkers that can be used instead of a clinical endpoint to show effectiveness of a product, a drug or a device, or whatever.

These are very controversial and very difficult to achieve -- a surrogate endpoint. And because folks confuse all

biomarkers with the surrogates, the chance for progress was very slim. So we have had numerous advisory committees and scientific discussions, and so forth, and have generally gotten everyone to accept the idea that what we need is the fitness for use criterion for use of a biomarker.

In other words, that the scientific data that is generated about the biomarker is adequate to use it for whatever you might be using it for. Are you using it to select a patient population? Are you using it to prevent people from getting an adverse event? And so forth. depending on what you use the biomarker for, you need a different type of data to support that use.

We're also -- because many of these biomarkers are going to be in vitro diagnostics or imaging agents, we're working across centers -- devices and drugs and biologics, for example, are working together on these issues.

Within the Center for Drugs, a formal biomarker qualification process has been set up, and an agency-wide process is being developed. And what we will do as we get these new biomarkers is we will post the data and have a public comment period on the biomarkers.

Right now, the new biomarkers we're looking at, we're undergoing a process, is a set of drug-induced nephrotoxicity biomarkers that have been submitted by the Predictive Safety Consortium to the FDA. And we are in the process of looking at those biomarkers. They have been qualified by that group for use in animal toxicology studies as more sensitive measures.

So once we complete our analysis we will post that publicly, post those data. And that way hopefully we can move toward public, scientific acceptance of new biomarkers.

Now, internationally, this has -- there has been a lot of interest as well in

Europe. They have an Innovative Medicines Initiative that they propose at funding for a very large amount of money over a number of years, and we are working with the folks who are doing the Innovative Medicines Initiative to make sure that our efforts are synergistic and not duplicative, but they also may come up with new biomarkers.

And the EMEA and the Japanese regulators are participating with us in our biomarker qualification process. So hopefully what we would have is new biomarkers for a variety of uses that would be accepted worldwide by the regulators.

And we are working in the ICH, the International Conference on Harmonization, on pharmacogenomics terminology.

Now, one of the biomarker -- one of the types of biomarkers that has moved ahead very rapidly in the past several years to a great extent because, of course, of many people like Allen out in the scientific

community, as well as by very heroic efforts I think by members of the FDA staff is pharmacogenomic biomarkers.

And these have the potential both to improve the efficacy as well as improve the safety of existing drugs and biologics that are out on the market as well as new ones that are coming along. So we have announced a relabeling of a number of drugs -- 6MP, irinotican, warfarin, codeine -- and you will soon probably be seeing more announcements of drugs where pharmacogenetic markers will improve the dosing of these drugs or reduce adverse events.

In the policy arena, we have also been working on guidances on new emerging type of in vitro diagnostics such as gene expression assays, and so forth, and this has of course caused a great deal of controversy, which many people are probably aware of, but we are continuing to move on in this area, because these type of new gene expression

assays, and so forth, will be some of the tools that we will use in critical path.

We have issued more guidance on pharmacogenomic data submission. Our data submission process, our voluntary submission process, is going very well. We have had over 30 submissions, and that is a collaboration across the FDA that NCTR is hosting much of the data from. And we are hearing about genomic experiments that are being done on numerous types of products.

We have recently opened this up, and now we're going to be getting proteomic, metabolomic, and other types of newer molecular experiments submitted to the voluntary process as well.

And there are multiple consortial efforts going on in this area, which I will discuss a little bit. Safety is important. We're going to be talking a lot about safety today. For pharmaceuticals and biologicals and medical devices, side effects don't happen

to everyone. They usually happen to a small subset of individuals.

And what causes a specific individual to have a side effect? That is one of the important aspects of safety that is often neglected in the goal of simply adding up the number of problems.

We need to improve safety through better mechanistic understanding, and this relates to critical path, because we finally have the scientific tools to understand why various people get various side effects. But we need to develop those tools and apply them to the development process. Otherwise, we're not going to learn.

And we think certain biomarkers may be low-hanging fruit. For example, genomic biomarkers -- one of the most prominent experiences has been with abacavir, and the fact that there is a genomic marker for immunologic -- it says here skin reactions, but it's really skin -- immunologic reactions

that lead to anaphylaxis, very serious reactions.

There also have been markers published for carbemazepine with Stevens-Johnson Syndrome in TENs, which are extraordinarily serious subcutaneous reactions from that drug.

As we said -- as I said earlier, there are genomic markers that look at folks that metabolize warfarin differently or differences in the target for warfarin. Warfarin is an anticoagulant. This story is rapidly evolving. We have relabeled warfarin, but we expect that there will be more information accumulating quickly about the proper use of warfarin, and we're doing this as one of our critical path projects as kind of a proof of concept.

And codeine also was in the news. Codeine doesn't work at all in some people, and other people it is very rapidly metabolized to morphine. In certain nursing

mothers, this may result in a serious toxicity to the infant or perhaps fatalities in some cases. So these are just examples of safety biomarkers.

Future opportunities -- I'm going to skip over this, because I see Ken looking at his watch here, and we have to move along.

The real issue here is: who -- what entity is charged with developing safety biomarkers? I mean, if we simply would leave this to academia as kind of a, you know, project of interest or research project or something, this isn't really going to get done. The real world requires we need to do concentrated validation studies or qualification studies to get these to the point where they can actually be used in clinical medicine.

There are several consortia that I've presented before. There's a Serious Adverse Event Consortium that is working on this. The C-Path Institute is working on it

with the Predictive Safety Consortium. And the Biomarker Consortium at the FNIH is also working to some extent on safety biomarkers.

But we're going to need worldwide collaborations to get the clinical data that we need, because especially with these genomic markers there is ethnic variability that occurs around the world in many of these, and so we need data from many populations to really understand the performance.

And we're going to be talking a little bit I think -- I will be talking a little bit about safety surveillance using health care databases. We need to link with those to be able to identify the cases, the people who are actually having these problems, and then be able in some way to test their DNA, so that we can really identify what the risk factors are for new problems.

Now, in cancer, we have a very good partnership with the National Cancer Institute called the Interagency Oncology Task Force,

and there we are working on a number of critical path projects. The Biomarker Consortium at the Foundation for NIH has a Cancer Steering Committee that FDA is participating in actively, and we are also working with two cancer groups -- the American Association for Cancer Research, and -- on biomarker development, and with ASCO, the American Society for Clinical Oncology, on clinical trials using these biomarkers. So these are all critical path projects that are occurring in the cancer area.

In imaging, the story is not as promising, unfortunately. Imaging is probably one of the most promising fields possible I think for advancement of development science, and yet we're having extremely slow progress. It's very frustrating, in my opinion.

Imaging -- some group ranked the top 20, you know, medical advances of the last century, and imaging was right up there. A couple of different imaging techniques were

rated as amongst the highest advances. But we need to do better in this area, so this is one area I think where we -- we have issues with the agency review function in imaging, and we have issues on the outside with the ability to develop imaging agents and standardize them.

The Alzheimer's Neuroimaging Initiative is going on at the Foundation of NIH for a number of years. That's one effort where there is actually concerted effort to look at the natural history of Alzheimer's using imaging biomarkers. Hopefully, this will yield important data that tell us how we can use imaging in Alzheimer's Disease in product development.

And we need a better way to support the use of molecular probes, which is the future of imaging. That is the intersection of molecular medicine with imaging, and to do that in product development. Right now, again, many of these probes are developed by a single company. They're used in development

of a single product, and then they are put on the shelf and they are available for general use ever again. And we are trying to make efforts under critical path to remedy this situation.

So I think I'll skip over this and talk a little bit about our clinical trial modernization efforts. Like all areas of critical path, there is a parallel. We need to advance the evaluative science, and then we need to modernize the regulation to match those scientific advances that we make. And those things need to occur in parallel. So there is policy development that has to occur, along with scientific development.

And nowhere is this clearer I think than in clinical trial modernization. And so we have focused to some extent on modernizing the regulations in this area, because the science is difficult and is moving slowly.

We have issued a number of guidance -- guidances out of the critical path office

-- exploratory INDs in '06, a final guidance on using computerized systems in clinical trials in '07. Obviously, if we don't move modern informatics into the clinical trial realm, we're not going to get anywhere with clinical data.

Adverse event reporting to IRBs, this is a very big problem for the IRBs. We put out a draft guidance, '07. Supervisor responsibilities of investigators, and using a centralized IRB process, and the FDA guidance for that. So these are all efforts to modernize and clarify the regulation of this scientific endeavor, in other words, of clinical trials.

We also have done a number of hearings. These hearings are a prelude to regulation changes, exemption from informed consent requirements for emerging research, adverse event reportings to IRBs, and then a direct final rule on GMPs, which are almost done with.

We also announced in '06 the BiMo Initiative, which is trying to modernize the way we -- our regulatory oversight of clinical trials. We recognize that in the United Sates doing -- executing a clinical trial and getting it actually done and reporting out the results is a very lengthy and very difficult process that no one is very happy with.

This is pushing the conduct of clinical trials overseas, and it also limits the number of clinical trials that are done. But if we can't do a lot of clinical trials, we are not going to be able to evaluate the impact of all of this new science that is being done on human health. We have to be able to do these trials, so we've got to do better at our execution and oversight of clinical trials.

To this end, we had a meeting with the Drug Information Association, defining and implementing quality in clinical investigations, because that's -- there are

two issues. One is quality, and the other is human subject protection. And quality is part of human subject protection, in fact. That was a very positive meeting, and I think there is common ground across many sectors in how to improve the quality and efficiency of the clinical trial process in the United States.

To this end, we are forming a public-private partnership with Duke, and we have signed an MOU with Duke. It was recently announced in November. This will to the end -- the public-private partnership will be assembled to the end of improving the quality and efficiency of execution of clinical trials.

We think that this is -- again, FDA only has a small part of this, but it's an essential part and we can kind of lead or move this dialogue along. I'll skip over the methodologic issues.

But, again, the lack of a really large academic support base in the United

States for clinical trial methodology and biostatistics applied to clinical trials means that this field hasn't moved as quickly as it should, and we need to have new clinical trial methodologies develop that are able to incorporate all of these biomarkers and other tests into them. These were primarily part of the adapter designs.

Bioinformatics is another issue that is supported by critical path. It's one of the critical path need opportunity areas. You'll hear about this this afternoon I think in a fair amount of detail from the Subcommittee report about the needs of the FDA. And the critical path initiative has set up ways of trying to address these to the best we can given our resources within the FDA, along with the CIO of FDA and the Office of Planning.

And we've set up -- which I talked to the Board about a little bit last time -- business review boards, and so forth. So we

have supported the Data Standards Council to develop a large number of data standards that are kind of -- they are the infrastructure that is going to be needed if we are going to pool data across multiple clinical trials, across multiple development programs, and actually learn and develop scientific information and knowledge from all of these development programs that are going on.

So I will spare you all the details of this, but we are hard at work in doing this.

What we learned -- and we learned something very important from the -- from our Subcommittee review -- we learned that what we really need to call all this is the information supply chain, that we at FDA have this information supply chain that we manage.

And I think this is very important, because we were never able to explain to people why it's important that we be able to describe this product out here in health care,

in this hospital, okay, and have an actual description of that and how that might impact on our scientific activities over here in NCTR, but it does.

That's the information supply chain, and what we are looking at, say, in the life cycle is how this medical device is impacting this person in this hospital who has an adverse event, and maybe it will go back to the laboratory of Larry Kessler or NCTR and we'll figure out, through genomic assay or whatever, what the root cause of that might have been, or some human factors analysis, or whatever.

So this is an extremely important concept of information supply chain, and we are working on this under critical path.

CHAIR SHINE: Let's just take five more minutes.

DR. WOODCOCK: Five more minutes. Okay, sure.

So the final part of progress is

the drug -- the product quality for the 21st century, pharmaceutical manufacturing. We are moving along on this. This continues to make progress, and we are right now working with Europe, the Europeans, to try to have a new process for changes in manufacturing that doesn't require so many submissions to the regulatory agencies.

This was one of the goals all along is that have the quality systems of the manufacturers be competent to manage change control without consulting the regulators every time any change was made. So we're working with the Europeans on this. Obviously, this will require worldwide collaboration of regulators, but I think this is -- this is where we really wanted to get with this initiative, and through many years of concentrated effort we're getting there.

We coined this term -- quality by design -- for talking about this, that you would really understand the critical process

and product parameters, so that you would have a design space that would allow for a lot of changes.

This type of science, manufacturing science, again isn't -- people really don't think of this when they think of biomedical science, but this is just as important as any other part of the manufacturing control and testing and evaluation of products, because fundamentally if these products aren't made in a reliably -- reliably and robustly and uniformly, then all of the other testing that you do is worthless.

Now, in 2007, we also expanded the critical path a bit. We had a critical path report issued for generic drugs issued in '07, and this described the scientific activities that would need to be done, particularly add new dosage, new types of dosage forms to generics, such as creams, inhaled products, and so forth. We don't have good models for how they would become generics right now, and

often they don't. They are big lacunae in the generic availability, and that increases cost for the public.

In addition, complex drug substances, those that aren't simple, are going to have a hard time becoming generics, and more science is needed there. And we also brought in everyone at FDA in an FDA-wide Critical Path Steering Committee to figure out the priorities for scientific projects.

So, in 2007, we also talked to the foods folks and veterinary folks about what they needed. You're going to hear a lot about this probably this afternoon on the need for new evaluative technologies in the food area. We're very well aware of this, and one of the interesting things I think the Subcommittee this afternoon will talk about is that currently the science and technologies is coalescing, so that gene expression or genomic tests or whatever are applicable to drugs, are applicable to foods, and so forth and so on,

and so are many of these technologies.

So back -- I'll just finish up here. The question of the critics is: well, has this really meant anything? Has critical path changed drug development? I think it has definitely changed the dialogue, and we have an unprecedented amount of collaboration going on worldwide now in many areas, including patient groups who are working alongside of us in medical societies, subspecialty societies.

The voluntary genomic data submission process is a big success. The manufacturing changes are successful and are making a demonstrated impact. And the consortia that have been set up, the collaborations, are also making scientific progress.

There is buy-in and enthusiasm and participation at FDA, but by no means is everyone convinced. They want to see the funding, okay? And so this depends in part on funding. The FDA Amendments Act, as Dr. von

Eschenbach said, was signed and includes an FDA foundation that was intended to help support critical path activities, but we continue to be on a -- and we are on a continuing resolution, and that hasn't been implemented yet. But we -- so currently we are mainly working with our external collaborations that are really continuing to grow.

I'm going to skip over this, because Ken said I should.

And let's see, I just want to talk a little about the criticisms of the initiative. People say this isn't tightly focused enough, it's too broad, it lacks a few specific compelling goals, and, therefore, they are not sure that all FDA staff is on board, or that funding can and will penetrate to all levels of FDA. And it is true, we -- well, so that's I think basically the criticism.

I'm sorry. It seems to be going

the wrong direction here. There we go. Okay.

We feel that real progress has been made with the critical path initiative, but we could do more with more. We have not really been funded until late fiscal year '07 where we received $5 million. That has been the funding so far for the critical path initiative, and some of that supporting the bioinformatics efforts I discussed earlier, some of it was given to the centers to support some of their research activities.

The agency is really taking a long-term transformative point of view with critical path, not a short-term focused win approach. And we'd be -- I'd be interested in what you think about that.

Our current practices have been in effect for about 20 years, and it is very difficult to change. But I think the way we've changed the manufacturing regulation, and actually the way manufacturing is looked at on the -- in the industrial sector over the

past five years has really been extraordinary. We have made a very significant change.

So the needed investments also take time, because they involve scientific research. We don't expect to have results in six months from projects that require scientific research.

So we have to commit to ensuring an engaged and modern scientific workforce. I think that is going to be part of the discussion this afternoon, but I would say that modern regulation is not just going to be enforcement. It's going to be science-based, because the products and the tools of development are very cutting edge science. And we have to be able to look the industry scientists in the eye and have our own science at the level of the science that we are regulating.

And we need to -- we do, though, need to articulate a transparent and sound plan for identifying, evaluating, and

implementing our critical path priorities, and we will do so in 2008. It has been somewhat an ad hoc process up until this point.

So thank you very much for your attention.

CHAIR SHINE: Thank you, Janet.

Comments from the Board? Questions from any members of the Board? Yes, please, Dr. Sasich.

DR. SASICH: Thank you very much for the presentation. Just one quick question. Can you give us an example where regulatory science has either prevented or delayed the approval of a new molecular entity? And this is exclusive of follow-on biologics or generic. As long as you don't have to divulge something that's commercial confidential information.

DR. WOODCOCK: Do you mean sort of lack of regulatory science?

DR. SASICH: Right. Where it is -- where it may have actually delayed or

prevented the approval of a new molecular entity.

DR. WOODCOCK: Yes, we think -- I would say this happens all the time, okay, because we have unanswered questions. What -- you know, what we started out -- what I started out with was that the lack of the evaluative science now, or the regulatory science, whatever you want to call it, is now impacting the development programs, not just FDA's ability to assess them, but actually the success of development.

And I think we see hundreds of cases every year where the uncertainties, not just in new molecular entities, okay, because we don't hundreds a year, but where the uncertainties at the end of the development program are such that we have to go and ask for more information or data and put the product through more cycles.

And often sometimes those questions are never addressed satisfactorily, and the

product cannot reach the market, because the questions cannot be answered. Other times there are simply long delays. Other times the uncertainties seem adequate, the product gets out on the market, but it actually turns out it hasn't been adequately evaluated, new problems arise, and these cause additional problems when the product is on the market.

Availability of additional tools, both to evaluate them before getting on the market, as well as surveillance after -- better surveillance after marketing would really ameliorate this situation.

CHAIR SHINE: Dr. Woteki?

DR. WOTEKI: Yes. I'd like to go back to the biomarkers work. On the food side, FDA has a very well-developed process for reviewing health claims that you might want to make about a specific food or a substance within that food. And that whole regulatory review process really rests on the availability of biomarkers, of risk for

disease, and how they are affected by the food or the substance and food in question.

And to what extent is the work that's going on on the qualification or fitness for use ideas with respect to biomarkers also being considered on the food side?

DR. WOODCOCK: Yes, they are closely related. As I said, we are trying to develop an agency-wide process for qualification of biomarkers. And we recognize that generally the biomarkers that are now used in the foods area -- I mean, there are several categories. One would be very specifically nutrition-related, and then the others such as serum cholesterol or whatever would have been long-accepted biomarkers by the medical community.

And so the question arises, how would you get new biomarkers in the foods area? Well, it's very much the same question as, how would you get new biomarkers in for a

drug or for a device or anything else? It's the scientific data and the qualification of that biomarker would have to go through a process of clinical evaluation.

And, yes, so the short answer is yes. We're involving the groups in CFSAN who are involved in reviewing the health claims, and we -- when we develop the agency-wide biomarker process it will definitely take into account the need for looking at biomarkers for health claims.

CHAIR SHINE: We're running a little bit behind, so I'm going to move on to the NARMS report. And then, Janet will be back on safety, and I'm hoping that -- if you've got some questions, make a note. I'm hoping that in that question period you can ask some follow-up to this as well.

As you recall, the Board was responsible for scientific review of NARMS. That material has been -- was obviously provided to NARMS, and Steve Sundlof is going

to give us a follow-up with regard to the outcome.

Steve?

DR. SUNDLOF: Thank you, Ken.

Yes, it has been about six months now since the report was finalized. I think the report issued on May 25th of this year, and so I just wanted to report back now on what progress has been made in carrying out the recommendations of the Committee.

It became -- just as background, NARMS is the National Antimicrobial Resistance Monitoring System. It is run by three different components. The coordination is through FDA CVM, but it includes CDC, and it includes USDA. It started -- actually became operational back in 1996, and then -- back then it was largely E. coli and salmonella, but since that time campylobacter has been added to the panel, as well as enterococcus and the new arm of NARMS, which is the retail meats arm that I'll talk about.

And each year samples are collected from both humans and animals and retail foods to culture these bacteria and then determine whether or not they are susceptible or resistant to a panel of antimicrobial drugs, and these drugs are selected based on their importance to human health. So that's background.

The purpose of NARMS is to identify changes in antimicrobial resistance patterns in zoonotic food-borne bacterial pathogens and certain selected commensal organisms. And having that information, then we can respond to unusual or high levels of bacterial drug resistance in humans, animals, retail meat, in order to mitigate further development of resistance.

And we also use information to assist us in making decisions on the approval of drugs. For instance, if we know that there is resistance issues associated with certain antimicrobial drugs, we take those into

consideration in determining whether or not those drugs can be approved, and we use it to design follow-up epidemiology and research studies to better understand how these resistances is developing and emerging and spreading.

So, again, the NARMS program is -- basically has three components. The USDA -- Agriculture collects information at slaughter on animals that are going through the slaughtering process, collect samples for salmonella and campylobacter for instance.

CDC is -- does the human component and looks at the state departments of health, submits samples, and they are tested, and then we at CVM are looking at retail means, actually going into supermarkets, taking samples of meats, poultry, and pork and beef, and running all of these same tests using the same equipment and the same means of analyzing the results.

So the Science Board -- the Science

Board Advisory Committee was established to evaluate the NARMS program and address four questions about the program that we had particular concerns about. The first one is the sampling strategy. Are the -- is the -- are the samples that are reflected, are they representative of the greater public in general? Or are there biases in how we are sampling?

Are the research studies that are being conducted under NARMS, are they the right research studies? Is there potential to do more, are we doing too much, etcetera?

The international activities, because more and more antimicrobial resistance is a global issue, it requires that there be a lot of international collaboration and cooperation. And then, data harmonizing -- harmonization and reporting, because there are three separate agencies that are dealing with this, a lot of times the data are not transferrable across, and could this be

improved.

So the Subcommittee met on April 10th and 11th of this year and heard presentations from NARMS partners and stakeholders, and the Committee report again was presented on -- actually, on June 14th by the Chair, Lonnie King. And thank you, Lonnie, for all the work, and I would also like to recognize the other members of the Subcommittee, including Susan Harlander, John Thomas, Glen Morris, Jim Riviere, Larry Granger, and Scott McEwen -- were the members of the Subcommittee.

General comments of the Subcommittee were that NARMS has evolved into a mission-critical tool for FDA that is absolutely essential in the work that FDA does. That the commitment and the dedication of the NARMS team is very laudable, that outstanding progress and acceptance has occurred over the last decade, since its inception, and suggests -- it was suggested

that visioning and strategic and business planning process be initiated.

And then, the suggested program should evolve and become more predictive, that there's a lot of potential here in the NARMS program to do things that are beyond what we're currently doing. It's underappreciated benefits for meeting the needs of veterinary and human medicine, and -- but that we were -- it was suggested that we keep the focus highly focused on public health.

And then, to develop a 10-year plan with a lot of involvement from the public. So here is -- here is our -- where we've -- what we've done to date in response to the report. We have held strategic planning meetings. These are ongoing.

The first one was held September 17th and 18th, and at that meeting this report was discussed thoroughly and with the intention that the -- to start the planning process, to start the visioning process, and

to look at both long- and short-term goals.

The discussions have continued. We will -- the next one will be in March at the infectious -- or emerging infectious disease conference meeting, and so this is an ongoing part of our response to the plan.

Sampling strategy -- we -- the Committee -- Subcommittee determined that there are inherent biases in the sampling strategies employed by NARMS and gave recommendations on how they could be improved.

And here is what the Committee found, that interstate and intrastate variability and the number of isolates submitted by clinical labs -- this is on the human side -- vary considerably. So there is quite a bit of variability in physician culture practices. In other words, when does a physician actually take a culture in order to determine what bacteria might be present and where the resistance might be occurring? So that's highly variable.

There is a -- it would be ideal if we had a national random sampling of clinical isolates, but the Committee recognizes that this may not be feasible. And then, options within the current sampling structure would be to stratify data where feasible and periodic activity -- active sampling of the clinical laboratories rather than the passive approach. And then, encourage monitoring of commensals from healthy humans rather than humans that are ill.

In response to that, the isolates in NARMS -- random sampling of all clinical isolates at this point is not feasible. There are multiple laboratories in every state, and it's just not feasible at this point in time to try and do a random sampling, largely because the resources aren't available.

Sampling of -- sampling in all states for salmonella is frequency-based, and that is good, and so that every -- one in every 10 salmonella samples is sent into NARMS

for doing microbial susceptibility testing.

But for campylobacter that's not the case. So there are some -- some frequency-based -- they may be frequency-based, but they are different, so in one state it may be all campylobacter, in another state it may be one in five, so that's inconsistent.

And continue to evaluate the sampling scheme and conduct data comparisons -- for instance, look at the NARMS data, which is a small subset of a greater database, the Public Health Laboratory Information System, which collects many more samples, and look at the NARMS samples compared to those bigger databases and see if they look like they're representative. If not, then we have some more work to do.

Resources are currently not available for targeted studies. We have to rely on -- we don't know what physicians -- what the variability and how physicians determine whether or not the culture -- and so

we're going to be relying on other sources of published literature, for instance.

NARMS is not stratified. In the annual reports, there is a large number of sites in the NARMS area. And some of them generate a lot of samples, some of them don't generate that many samples. Many sites have very small numbers, and there's a lack of detailed demographic data at some of the sites, so we don't really know a lot about where the sample originated.

There is an article and articles that are under development that look at the distribution of clinically important multi-drug resistant salmonella isolates. So, again, we're going to have to go back to literature in order to determine whether or not we think the sampling is biased or not.

If there are more -- if more resources became available, we would like to expand the catchment area for campylobacter and look at testing for commensals in non-

diarrhetic humans, in other words healthy humans. That's on the human side.

Now, on the meat -- retail meat side, the Committee determined that this was extremely important data to have, because it's the closest that you get to the actual consumer. Samples are from a limited number of areas and a small number of products.

Lack of national sampling strategy limits broader interpretation, and it was suggested that it may be more useful to adjust the sampling strategy to look at specific hypothesis-driven questions, recognizing that we're -- the resources available are not going to be sufficient to get a really robust sampling of the entire retail market.

It was agreed that retail meat surveillance is very important. That's what -- we agree with that recommendation or that comment by the Committee. The data provides -- it provides data on prevalence of enteric bacteria in retail meats and the prevalence of

resistance. The data are used to support the evaluation of new animal drugs. This is our Guidance 152.

We do use this information that we obtained from retail meats, as well as the other parts of NARMS, to look at what kind of baseline resistance is out there, and then make some determination whether or not the introduction of a new antimicrobial may in some way drive that resistance.

And then, it's very useful again for monitoring resistance if we do approve a drug, and that way we can -- we can determine what effect it is having.

It provides a source of retail meat isolates, so we can compare human isolates to improve our understanding of the contribution of retail meats to infections in humans. Again, it's the closest that you actually get to the consumer. It's the last step is the food-to-fork -- farm-to-fork chain, and so it's -- the information is very useful to us.

Sampling is limited by availability of resources and personnel. We did have -- Pennsylvania joined the program in July of 2007, so that is increasing some of our sampling geography. Maryland we think is rejoining, and so, again, there is another state that will be involved in it.

We may reduce the testing of ground beef and porkchops, because there is -- out of all the samples we may have one or two out of thousands of samples that actually are positive for campylobacter and salmonella, so take those resources and put those against some other foods like poultry that -- where the incidence is quite high.

And then, we are also looking at pilot studies where we are going to compare different kinds of meat. For instance, with or without skin and bone in poultry may have a significant impact on the bacteria present. Other pathogens that we think are going to be important in the future -- clostridium

difficile, thinking about adding that, and MRSA, multi-drug resistant Staph aureus, is obviously one that is very important these days.

So those are two areas where we're thinking of expanding. Also, looking at turkey parts and seafood. We're not there yet, but those are the ones that we're considering for future use.

In terms of the animal side, the live animal side, the part that USDA is responsible for, slaughter samples, samples from the pathogen reduction HACCP programs that USDA FSIS conducts are biased, because the plants are not randomly selected. And it is actually going away from random selection. FSIS is now going to be targeting those plants that have the biggest problems for more intense sampling.

So we will be less random in the type of samples that are collected under that program. Now, the clinical diagnostic

laboratories that basically uses samples from diseased animals are not very germane to actual looking at the public health aspect.

NAHMS, which is the National Animal Health Monitoring System, and other on-farm data that can be potentially used is limited because they are not representative, generally, of a national program. And they are sporadic, so that one year we may be looking at cattle, three years you might be looking at pigs. It doesn't give you a continuous look at what's happening in the microbe world.

And the recommendation was to encourage other pilots, in collaboration with the animal health and food safety epidemiological program, another USDA program that is not -- we are looking at that, but right now there is not a lot of funding for that program, so there is not going to be a lot of data generated, at least in the near future.

Samples from the FSIS slaughter samples provide for ongoing monitoring, and in June FSIS moved to a more risk-based inspection. I already talked about that. We are looking at -- FSIS is also looking at some studies where they are looking at background information, just take some snapshots and get some background information, a raw ground beef component baseline study, is scheduled -- is completed, and this year there is a young chick and broiler baseline study in progress to get a kind of a representative idea of what is actually occurring, and then a young turkey and market hog baseline studies are anticipated for 2008.

So we can take the HACCP studies or the general HACCP samples and look at the frequency and compare them to these baseline studies and determine whether or not those HACCP samples that are coming through at slaughter are actually representative of what they're seeing in baseline studies.

And then, we'll have ongoing discussions to explore alternative sampling strategies including taking samples from the NAHMS studies and the CAHFSE studies. So that's -- that was a sampling.

Then, we also asked the Committee to evaluate the research that is conducted under NARMS, and are there epidemiological or microbiological research studies that would better serve the goals of NARMS. And in that we -- we looked at an active research program.

The Committee found that an active research program is critically important to the continued success of NARMS, and these are the areas where they suggested further expansion, and that would be laboratory methods, standardization of laboratory methods, platform development, and some pilot projects, to expand the hypothesis-driven research with an emphasis on assessing human risk and to encourage more collaborations and partnerships and gain understanding of flow of

resistant genes and bacteria across the farm-to-fork continuum.

So NARMS is actively involved in research to try and standardize the laboratory methods. This has been very important, and it has been -- the payoff has been very rewarding. Not only are we looking at standardization -- standard methods for culturing, but also looking at some of the new techniques for identifying organisms through PCR microarrays and molecular serotyping.

The platform development, we're linking NARMS to data -- susceptibility data with PulseNet, and sequencing the salmonella genome with Craig Venter Institute just down the road here, and then ongoing studies to better understand cross-resistance, linked resistance, and transfer of resistance determinants in both pathogenic and commensal organisms. So research into how these determinants of resistance are moving among the microbial world.

And then, to do -- we're looking at some of the pilot projects that we are looking at again. I mentioned MRSA and clostridium difficile, thinking about adding those to the NARMS, enterococcus strains in humans and local food and farm animals, and targeted resistance profiling to help answer regulatory questions.

CHAIR SHINE: Steve, five minutes.

DR. SUNDLOF: Okay. Thank you.

The research studies -- again, NARMS research projects are driven both by hypothesis testing and the need for new methods, continued studies on the burden of illness, what are the actual harms that result from exposure to resistant bacteria.

And we are looking back at historical strains, so we're looking at some of these libraries of bacteria that were around at the time when new antibiotics were approved years ago, and seeing if there's a relationship between resistance development

and the approval of those drugs, and looking at some other methods, the newer methods, multi-locus sequence typing and others.

Continue to enhance -- we are continuing to enhance collaborations with NARMS partners, and we are looking at our academic friends and then others to help us with the research. Also, we have numerous collaborations with other government organizations and with the international community.

And that brings us to the international activities. How is NARMS doing in terms of relating to the broader international issue of antimicrobial resistance? And, again, it is a global problem. There is strongly endorsed -- the Committee strongly endorsed continuation and expansion of our international programs, our need to improve coordination of NARMS components internationally for purposes of creating a global system, a global model using

NARMS as the model, and then continuing the need to adopt new technologies and ensure quality data and timely reporting.

NARMS is committed to supporting international activities. We contribute to the WHO global salmonella surveillance support system, and we are helping with training of other countries, especially China, to develop similar systems. We collaborate in North America with ResistVet, which is a Mexican counterpart of NARMS, and CIPARS, which is the Canadian counterpart of NARMS.

And we are -- we are enhancing the network development, the international network of integrated surveillance for antimicrobial resistance and enteric bacteria, being developed as a forum for communication on harmonization.

Just as an aside that's not here, we also participated in the Codex Alimentarius Task Force last month held in Korea on antimicrobial resistance, and this task force

has been established to develop risk assessment and risk management guidelines for countries in dealing with this issue of antimicrobial resistance.

Data harmonization and reporting -- our current plans are for more and more harmonization. We're getting there slowly but surely. Again, the data resides in three different agencies, but we're coordinating that across the board. We are getting much better with the help of David White and Beth Karp of getting these reports out in a much more timely manner, so we will continue to work on that. We think that's very important.

I'll kind of skip through here. I did want to go through this, and I guess I'm going to need Carlos' help on this. Just to show you some of the data, how we've been managing the data lately, and so I'm not sure what I do here -- let me just go -- okay. So let's take a drug like gentamicin, for instance, and we can take gentamicin, look at

it in the various animals and retail meats, so why don't we click on chicken breasts for instance.

Okay. Ground beef -- let's try ground beef. Okay. Unfortunately, this one -- let's try a different drug. Let's go to cephalosporins. You can go down here. Okay. And let's try ceftiofur. You only have that from the last two years.

Dave, do you have a drug that we've had since 19- -- or since 1996?

DR. WHITE: Yes. If you pick one of the animals at the bottom, it will give more data.

DR. SUNDLOF: Okay. Oh, okay. I'm sorry. That's right. We were just -- I was just dealing with retail.

Try chicken. Okay. And then, turkeys and cattle. There we go. So you can look at these -- the data over the years, and you can see trends in antimicrobial resistance, and it looks like chicken in this

case is going up. Is that right? I can't read those colors. I think I'm going color-blind. No, it's actually cattle, I believe, is going up over the years.

So this allows us to look at various antimicrobials, and it allows people access to this, so they can get trend information over time. And so this is just one of the examples of ways we're trying to do a better job on the reporting part.

And I know I've run over, Mr. Chairman. I apologize. But I would like to, again, express my thanks to the Committee for doing an outstanding job.

CHAIR SHINE: Thank you, Steve.

And I do want to give Lonnie and members of the Committee to comment with regard to the program's response to your review. Lonnie, do you want to start off, just --

DR. KING: Sure. Thanks, Steve.

Really appreciate that report and

the updates, and also compliment you for the progress the activities are taking, especially in the areas of research. I think those are some really good suggestions and actions.

One of the things that came up that I know you didn't probably have time to cover was the need for interoperability of the data, not only sharing amongst the three agencies that are involved, but also to make it more accessible to researchers outside of the agencies to kind of leverage research. Have you given any more thought to that? And could you respond to that?

DR. SUNDLOF: Yes. I think one of the issues that we are continuously working on with all of the NARMS partners is to try and make that information accessible. This information that I just showed you will be accessible to everybody, so anybody can go in and look at the information, the entire amount of information that has accumulated.

Now, making the individual data

available I think is something that we need to put more effort into to make sure that -- you know, that anybody that wants that information has access to it, to do more hypothesis-driven research. So I think we are -- we are making progress.

It's -- when we started out, for the first few years it was just a disaster in terms of everybody having different information that nobody could -- you know, if I wanted to look at CDC's information, it was very difficult. If CDC wanted to look at USDA's, it was very difficult. And we've come a long way in making that more homogeneous.

CHAIR SHINE: Susan?

DR. HARLANDER: I noticed as you showed us the demonstration that the data that you have goes through 2003, and I think that was, you know, one other thing that the Committee was very concerned about is, if we are really going to be using this information to drive drug discovery and many other kinds

of things, that a three- or four-year lag in having access to that information is an issue.

And, you know, I notice that you are addressing that, but I guess personally as a member of the Committee would really encourage that the timely publication of that data, as well as the searchability of it, and the availability, to industry that will be developing those drugs is extremely important.

DR. SUNDLOF: Yes, thank you. And I'm happy to report that we're making rapid progress on it. And, Mike, can you -- or, Dave, can you tell me where -- where we're at in terms of getting the annual reports out?

DR. WHITE: Sure. Just to let you know, we also this summer hired Dr. Beth Karp as a new position, the NARMS Coordinator position, and that is a position that has been vacant for about three years. And her major responsibility is putting together the executive report, which is going to be the report that puts together side by side the

retail data and the animal data and the human data.

As Dr. Sundlof mentioned previously, typically what has happened with the NARMS is there has been three annual reports by each of the three participating Federal Government agencies. We have created now an executive report which puts it all together. And if you look at web hits on our website, it's 1,000-fold higher for the executive report than the individual reports. So we're moving toward that, and Dr. Karp's responsibility is putting that together.

The '05 annual report is going in front of our central management next week for approval. After that, it will be two weeks probably before it's released. CDC is working on the '05 report as well, and we're working on the '04 and '05 executive reports as we speak.

So with the addition of Dr. Karp, we have doubled our NARMS group by two, 50

percent from myself to -- myself and Dr. Karp, but we work -- working much better together as a team with all three federal agencies. So we're making progress, and I expect in the next two years to be as caught up as we can be in terms of real time surveillance, probably at least a year behind to 16 months behind.

CHAIR SHINE: I see John Thomas sitting there. John, you wanted to commend?

DR. THOMAS: Yes. John Thomas. With the globalization being mentioned on several occasions, I think the trading aspect of some of these countries that are bringing food to the United States shores is extremely important. And I don't know where the resources are going to come from, but it's extremely important that other countries be brought into this loop.

DR. SUNDLOF: Yes. Thank you for that.

And just this year we have issued an import alert on Chinese shrimp, largely

because of the use of fluoroquinolones and our concerns about resistance. So it already is having an impact on international trade.

And one of the areas we think is ripe for expansion is to look -- start looking into seafood as a possible vehicle for spreading antimicrobial resistance. So thank you.

CHAIR SHINE: I want to again thank Dr. King and his Committee for the review, the NARMS for a response, and we will follow with considerable interest.

Thank you very much.

We're going to take a break until 10:30, make up a couple of minutes, and we'll start promptly at 10:30 and see if we can get back on schedule.

(Whereupon, the proceedings in the foregoing matter went off the record at 10:20 a.m. and went back on the record at 10:31 a.m.)

CHAIR SHINE: Understandably, there

has been no subject of greater interest over the last couple of years to the Science Board than the issue of drug safety, and we're pleased that Janet Woodcock is going to give us an update on drug safety. In the question period, there will be an opportunity also for follow-up questions with regard to the critical path presentation.

Janet?

DR. WOODCOCK: Thank you again. What I'm going to do this morning is not do a slideshow but actually talk about the recent developments. We've talked to the Science Board in the past about the IOM report on drug safety, about the subsequent reports, and so forth, but very recently, as you heard from the Commissioner, the FDA Amendments Act was passed. And this is a voluminous statute, but it has a very large section devoted to drug safety.

It also added $25 million additional in user fees for drug safety

activities, and it authorizes an additional $25 million to be appropriated -- but that has to be done by the appropriators -- to carry out the drug safety section that was passed in the statute.

Now, CDER -- I'm speaking now as head of CDER -- CDER's prior commitments included the response to the IOM report and the subsequent reports and activities by the IOM on drug safety, as well as the GAO and other plans that the agency had made.

Currently, these are all being crafted into a unified plan that will incorporate these activities and actions with the drug safety elements in the Amendments Act, because the Amendments Act calls for -- upon the agency to do a large amount of activities.

It has a lot of procedures, and so forth, and so we will put forth a comprehensive plan early in '08 about how we will address all of this as a whole, as a

single effort rather than separated efforts responding to the IOM and to the Amendments Act, and so forth.

So first I want to talk to you about Title IX of the Act, which is entitled "Drug Safety." And I think this is really a ground-breaking statute in the sense that it has been many, many, many years since the Congress opined in law about post-marketing safety of drugs.

A long time ago the reporting requirements were put in for post-marketing adverse event reporting, and that was simply the structure that we see under what you consider maybe MedWatch or AERS, the Adverse Event Reporting System, where people send in reports and the companies have mandatory reporting requirements of adverse events. That was basically what the statute said about drug safety.

And now I think with the passage of this Act we get a much greater emphasis on

post-marketing period and the performance of products in the post-marketing period versus the previous statute that was mainly addressing drug quality as well as the pre-market requirements for getting drugs and biologics onto the market.

So how is this new statute structured? What actually do they address? Well, first of all, there are three new authorities that are put into the statute. One is the authority for the agency to require post-market epidemiologic studies or clinical trials -- require them under certain circumstances which the statute goes into.

The second authority is the ability of FDA to require sponsors to make safety-related label changes, so FDA can order sponsors to change the label to include safety information under, again, certain circumstances that are outlined in the statute.

And the third, the agency can

require sponsors to develop and comply with risk evaluation and mitigation strategies -- and these are called REMS -- within the Act.

Now, FDA had some authorities related to this that were embodied in regulation before the restricted distribution parts of our regulation, and I'll explain this a little bit. This actually codifies this in a statute.

And these authorities don't take place for 180 days, so they're not in effect right now. They will go into effect, and they are pretty much self-executing, although we're going to have to figure out which ones of these are going to require additional guidance or actual development of regulations.

So let me talk about the first one, Section 901, post-market studies and surveillance. Now, in effect, FDA has always negotiated with sponsors and called for studies to be conducted post-marketing when there were problems or even at the time of

approval there were post-market commitments made.

But for a variety of reasons these weren't always accomplished in a timely manner or, once a drug was on the market, the agency had difficulty reaching agreement with sponsors on additional studies that had to be made -- done. And the agency's only tool at that time would be to remove the drug from the market.

So this provides a new set of authorities and tools for calling for these studies. So the FDA may require studies at time of approval or after approval if there is new safety information. And the requirement must be based on scientific data and is limited to certain specific purposes to assess a known serious risk related to the use of the drug or to assess a signal, which is very common, of the serious risk that arises post-market, or to identify an unexpected serious risk when available data indicates the

potential for such a serious risk.

So there has to be a reason. That's really -- and, obviously, Congress was concerned about capricious placing of these requirements on sponsors, and, therefore, laid out a series of caveats or requirements that the agency would have to fulfill, more or less conditions, before this could be required.

It is limited to prescription drugs and biologics, this particular provision. And before -- and the caveats go on. Before requiring a study, the agency has defined that the current adverse event reporting and active surveillance system that is also in the statute that I'll get to in a minute, but that these entities, these methods, will not be sufficient to meet the purpose, these three purposes I just described.

And before requiring a clinical trial -- and the clinical trial is obviously viewed in the statute as the most onerous type of requirement -- you have to conclude that

the reporting requirements, the surveillance system, and an epidemiologic study, none of these would be sufficient. Okay?

And then, if this happens and a requirement is placed on a sponsor, then the sponsor has to submit a timetable for completion of a study as well as periodic reports on progress. And there is all sorts of, you know, stipulations on what the sponsor needs to do. And this is in response I think to the perceived problem that these studies, once agreed upon, were not completed and executed in a timely manner.

So this will have a timetable throughout the course of the study -- how much enrollment is there, how -- you know, how far has the study progressed, and so forth. It will have to be submitted to the agency.

And then, there is enforcement here that says if sponsors violate this, they can't market their drug, basically. They can't introduce a drug into interstate commerce if

they are in violation of this provision. And they may be in violation if they fail to comply with this timetable or any other requirement of the section, unless they can demonstrate some good cause.

Now, we all know from a scientific point of view sometimes it's very difficult to enroll people into a study, particularly if the product is already on the market and approved. People may not want to be in a study where they don't get the product, depending on what the product is. So FDA has to determine whether or not the good cause is good enough.

Now, the second provision is safety-related label changes. Now, FDA -- just like the prior provision, FDA could not mandate a label change to a drug or biologic. FDA would have had to have pulled it off the market. That was the recourse the agency had.

I think Congress and the media and everyone never really understood that we

lacked these powers, so this provides new authority to require labeling changes based on safety, new safety information with strict timelines for negotiating changes, because it's not that these changes didn't occur in the labels, but sometimes the sponsor and the FDA did not agree on the safety signal and there was a very prolonged time period wherein such label changes, safety label changes would be negotiated between the FDA and the sponsor.

And this, of course, made the clinical community very unhappy as well as patients, because here they didn't know about the safety information that was being discussed, and they were out there prescribing the drug or taking the drug.

So this, again, applies to prescription drugs or to a generic if there's no innovator that's marketing. And we have to promptly -- we, FDA, in this part of the statute have to promptly notify the sponsor when we think new safety information reaches

this threshold, okay, that might have to get in the label.

And, of course, that's probably an area where we need to develop some guidance or whatever. That's a gray area. When we see thousands and thousands and thousands of signals every year, when has one reached this threshold that we think it should get into the label?

After notification, then the sponsor must within 30 days either submit a supplement that contains a label change or notify FDA they do not believe a label change is warranted and why not.

And then, we have to promptly review this, and discussions may not extend for more than 30 days after the original notification unless FDA decides an extension is warranted. So this remarkably decreases the time of back and forth and negotiation about label changes for safety.

Within 15 days after the discussion

is over, the FDA may issue an order directing the sponsor to make whatever label changes FDA deems appropriate. And within 15 days of receipt of the order, the sponsor must submit a supplement containing a label change, and then with five -- within five days the sponsor may appeal using dispute resolution procedures, and there is all sorts of elaborate dispute resolution procedures in this -- actually in the statute.

Okay. Now, so this is important, but I think you can also see how important it is for us to all go as a group to a paperless label, because if we're having paper labels out there they, for the next year and a half probably floating around, depending on the expiry period of the drug, will have erroneous safety information in them.

And we have -- I have spared you the great details, but FDA has been working for years to move to a system where we get away from the paper package insert, and it is

all based on computers. This would allow these label changes, then, to go right to the pharmacy, swipable, with a bar code, and the label comes up with the new safety information in it.

Otherwise, we'll be in a very difficult situation of maybe sometimes having to recall all of the stuff, repackage it with new labels or whatever, which, you know, is totally inefficient both for health care and for everyone else.

So enforcement -- if the company has not submitted a supplement within the 15 days, or within 15 days of dispute resolution, the same enforcement mechanism applies, as I mentioned earlier, which means it can be -- you cannot market the drug in interstate commerce.

Now, to help us out in making our standards, Congress provided definition of new safety information, which would reach this threshold. Information derived from a

clinical trial, an adverse event report, a post-approval study, or peer reviewed by a medical literature, derived from post-market risk identification analysis system in this system is something that's set up in the statute that I'm going to talk about in a minute, or other scientific data deemed appropriate by the Secretary about a serious risk or an unexpected serious risk associated with use of the drug, and it goes on, or the effectiveness of any risk management strategies.

So part of new safety information might be that the risk management strategy is failing, and that additional measures need to be taken. So, and this goes on in some detail. So those are the first two, the ability to order new things, label changes or clinical studies, with significant penalties to the firm if this doesn't happen.

The third one -- risk evaluation and mitigation strategies -- is actually an

authority that FDA felt it had but not everyone shared that opinion. So this applies to prescription drugs and biologics, and is the set of risk management strategies over and above what you do for any ordinary pharmaceutical that was out there.

So in the pre-approval situation, the statute says that FDA may determine REMS is needed to ensure that the benefits of the drug outweigh the risks, and, if so, the FDA then informs the sponsor and requires a REMS -- risk evaluation mitigation strategy -- to be submitted.

And there are a whole number of factors that the Congress said should be included, so this recognizes the fact, say, that a cancer drug is going to have like a tremendous number of serious side effects, and so forth, and you wouldn't put extraordinary restrictions around the cancer drug, because basically the treating community understands that and will use the drugs appropriately,

whereas a headache drug, if it has some very special serious adverse event, you might have a fairly extraordinary system around it to make sure it isn't misused. So they go through all this.

And then, post-approval, if no REMS is in effect for a drug, the FDA may determine that REMS is needed and require the sponsor to submit one if there is, again, new safety information as described in the statute.

And then, the sponsor must submit within 120 days, or sooner if the FDA decides that's necessary for the public health.

Now, the elements of REMS, the only -- the risk evaluation and management strategies were actually dreamed up by FDA in the '90s to address risky drugs that were nevertheless needed by the population. And sort of the poster child of that was thalidomide.

So along with the sponsor of thalidomide a risk management strategy was put

into place to make sure that pregnant women wouldn't get exposed to thalidomide, okay, and since that time a number of these have grown. There are a number of risky drugs that have special problems, but that another -- a group of people may benefit from, but you need to manage those drugs in some special way that isn't normal in the health care system.

So the only thing that's required -- so there's a lot of flexibility with this REMS, in other words, because what you do to make a drug safe depends on what the risk is, and pregnant women is one thing, narcotic abuse is another thing. So there is all sorts of things that need to be done depending on what the problem is.

So the only required element in the statute for REMS is a timetable, and that timetable is a timetable for evaluation of how effective the risk management strategy is, and that's a good thing. I think, again, we have been very pressed for resources at the FDA,

and we have difficulty evaluating the effectiveness of these strategies, also because, again, the tools, the scientific tools for evaluating the effectiveness aren't really out there very well.

And hopefully maybe some of these pharmacovigilance systems that the statute also calls upon us to establish will provide the tools for us to see how well these things are working out in health care. So anyway, the only thing you have to do in the REMS is the timetable.

And then, here's the menu of things that could be contemplated. Med guides -- a med guide is something for the patient, that tells the patient about the risks. A communication plan might be one, such as letters to the health care providers or educational programs or whatever.

And then, restricted distribution, so that you can -- the drug would only be safe used in certain hands, for example, given to

certain -- maybe an in-patient situation or at a clinic to treat addictions or something. You know, you can think of a wide range of restrictions that you would do depending on the kind of drug that it is.

So we're allowed to require these restrictions, but there are caveats here. It must be commensurate with a specific serious risk listed in the label. So we can't be going on -- FDA can't be putting on all kind of restrictions unless there is a fairly serious risk. Of course, that's in the eye of the beholder. It may not be unduly burdensome on patient access, considering patients with serious and life-threatening diseases or people who have difficulty accessing health care.

This is a real issue, and in fact what we have found, which I think is something all policymakers need to keep in mind, is if we restrict access too much the patients will go on the internet and they will get the drug

without any health care intervention whatsoever, and that is an extraordinarily risky situation, since they may not get the real drug, or, if they do, they may be taking a very risky drug without any oversight from a health care practitioner. So we have to walk that line fairly carefully.

And then, we're asked to make sure that these risk management systems, whatever they might be, are more -- become more homogeneous and standardized, and that would be obviously extremely useful, because we're going to create more errors than we prevent, if we have 50 different systems for restricting drugs that pharmacists and hospitals and everyone have to implement.

The problem with that, then, we have to get various commercial entities to work together to collaborate on a standardized system for restricting access. But Congress calls upon us to do that, and we have done that. In certain situations that has been

effective.

So how -- what types of restrictions are being contemplated? Congress goes into this as well. You could restrict to health care providers who have particular training or experience or special certifications. We could restrict to pharmacies, practitioners, or settings that dispense the drug and require them to be specially certified. The drug could be dispensed only in certain settings, or patients could be subject to monitoring or have to be enrolled in a registry.

And, actually, we have done all of these in one flavor or another already, depending on the type of harm or problem that we're trying to mitigate. And then, we have to talk to our advisory committee about -- and to others, to our disarm advisory committee about standardization and try to pursue this, and then pursue evaluation to make sure that these restrictions are not unduly burdensome

to health care and to patients.

So now drugs -- as I said, we've already done this, so the drugs that are currently under these will be at some point, which we're trying to determine -- the legal issues are difficult, but at some point they'll be deemed to have a REMS. And so all of the drugs that have already been under restricted distribution and any one drug moving forward will all be under this REMS scheme.

And for the final piece of enforcement is civil money penalties are in the statute. And, therefore, anyone who violates these sections shall be subject to a civil money penalty, and there is a scheme of prices -- of costs for the fines in the statute. Okay? And the longer you fail to conform to the requirements, the higher the price tag goes.

Now, the other section I wanted to talk about briefly has already been alluded to

in this part about these new authorities, and that is pharmacovigilance and active surveillance. The Congress is very interested in FDA setting up a system that is able to utilize more or less real time or in reasonable time information from health care databases, including billing and claims data, transactional data, and e-health record data.

And the statute says FDA must, through collaboration, develop methods to obtain access to these data sources and develop validated methods for establishment of risk identification and analysis system -- is what they call it -- to link and analyze safety data from multiple sources.

Now, I think this is a tremendous scientific opportunity. Many people have been talking about this. It is technologically doable. It is simply required -- the governance and structure of this has been, you know, unknown up until this point. So Congress is telling us to go ahead and set

this up.

And this is something that we have been contemplating under this what we call a Sentinel network. The goal is that the system will include 25 million patients by 2010, and 100 million by 2012. I think this is modest. I think this could be easily exceeded very rapidly, if we can get the right people at the table.

And then, we have to -- Ken is telling me I have to move ahead, so I'll just tell you that this is a tremendous opportunity, this pharmacovigilance, and we will take advantage of it. And hopefully we will, you know, be announcing within the next few months how we're going to do this.

The formation of the Reagan-Udall Institute -- Foundation for FDA that allows us to -- would allow them to set up public-private partnerships may provide a very good venue for doing this. In doing this activity, FDA will need to partner with the data

holders, and the data holders are mainly the health care systems themselves that have the patient data.

Obviously, they are motivated to make their patients safer and to have the most efficient and safe health care possible. And FDA has the authority, then, to utilize those signals to make changes in drug labels or devices or whatever needs to be done, and we hope to build a synergy there.

At some point, I know you're the Science Board, so this is -- this will be information science, but I would like to quickly link this to the basic science, because what we need to do is not only find out who these events are occurring in but why are they occurring. And we actually do have the scientific tools now to find that out as well, and it's a whole range of issues all the way from human factors to pharmacogenomics that we can investigate.

So the statute also reauthorized

the Prescription Drug User Fee Act, and pertaining to drug safety additional monies for post-marketing activities were included in that reauthorization. And it removes the limitation that was previously in the User Fee Act, or I think it was three years after approval there was this window that those monies could be used for, and that restriction is now removed and the money could be used at any time.

FDA did analyses that showed that actually the burden of activities of relabeling and all of this continued for a very long time after drug approval. We continue -- and this gets to Larry's question earlier -- we continue to learn a tremendous amount about drugs for a very long time after they are put on the market.

So I will finish now. So the bottom line here is that as a result of the user fee program, and so forth, CDER -- the Center for Drugs -- once the budget is passed

by Congress will have an infusion of new resources to address drug safety. And there are key points that we will be focusing on. As I said, we'll come out with a plan of how we're going to do all this early in '08.

Post-market surveillance has to be enhanced, obviously. We are in the process of redesign of the AERS database, and an agency-wide reporting system, so people can report to FDA for any medical product. They can just report to one place and it will go to the right database within the agency. So we're in the process of doing that through the BRB.

We need to set up the process for pharmacovigilance that's called for in the statute, as I just described, and this fits in well with our -- which we have worked up very carefully -- the concept of the Sentinel network. We need an advanced computational infrastructure and support, and I think we'll be hearing a lot more about that this afternoon.

We are increasingly using large databases. There is no other way to figure out the performance of these products in the real world. You have from Steve about, you know, antibiotic resistance, and so forth, or in the health care systems, without the use of advanced informatics and large databases.

But we also are seeing increasingly the use of meta-analysis as a way of looking at -- evaluating signals. This also requires advanced computational infrastructure that we don't have right now at the FDA, and so we'll be planning to build that.

We'll need additional staffing in post-marketing, and we're going to need to write a great deal of policies and procedures, including the roles and responsibilities between new drugs and the Office of Surveillance and Epidemiology, and incorporating all of the new procedures that are in the Amendments Act that are spelled out in there. It's a very procedure-intensive

law.

And, finally, we need to focus on risk communication, another science that needs to be advanced. And we have recently published the first edition of our new safety newsletter, and we will continue to be doing that, as well as health professional and consumer and patient information sheets on emerging safety issues. So you probably have all seen these in the press about emerging safety issues, and I think, you know, this is going fairly well.

We are communicating earlier about these issues before they are really resolved, and that is a double-edged sword, of course, so we will have to keep evaluating how that works.

So that's an update on our safety activities and probably at the next Science Board we'll be able to explain our plan for dealing with these provisions of the Amendments Act.

Thank you.

CHAIR SHINE: Dr. Woodcock, thank you.

Please, we've got time for questions. David? Dr. Parkinson?

DR. PARKINSON: These are really interesting new authorities.

CHAIR SHINE: Want to pull the mic up a little bit?

DR. PARKINSON: Yes, sure. I'm just saying that the authorities are very interesting. And they raise the question for me, just as I consider efficacy and safety to be on the same biologic spectrum, the real question is: at what point do efficacy considerations fall under these authorities?

So, for example, let's say you had no information from the clinical trials that it continued to be conducted on these molecules. That in fact certain subsets of patients, as defined by the original label, have no chance of responding. Does that

become a safety issue? And does it fall under the REMS authority? This probably has not escaped your attention. I'd be interested in your thoughts.

DR. WOODCOCK: Yes. The question is that at the end of the day, what we're making is a benefit-risk analysis.

DR. PARKINSON: That's right.

DR. WOODCOCK: Safety cannot be considered absent the idea of what the benefit of an agent is. And Dr. Parkinson's specific question is: if you become aware post-marketing that a drug perhaps is really targeted or should be targeted toward a subset of individuals, and there is no evidence that in the broad population as defined in the label the drug is overall effective, what would FDA do?

I don't know. I can't say that I do not believe this is the kind of situation that was contemplated by those who wrote this legislation. They were thinking of

traditional adverse event type of safety problems. So I think, for example, the Hatch-Waxman statute, which was passed in 1984, and was fairly short and clear compared to this statute, we're still litigating it. Okay?

Every month or so we have a little Hatch-Waxman law, okay, so I think we're just starting down the path with this legislation of we're going to do the clear things that it calls for, we're going to execute those, and then we're going to have to see about these long-term implications, because nobody knows at this point, you know, what all of the final interpretations will be. And some of those will be decided by the courts.

CHAIR SHINE: But the presumption is that every agent has some side effects, so that if you had a population which had no benefit, but side effects, it's hard to escape that, ultimately become a safety issue. But it will be interesting how that resolves.

Dr. Roses?

DR. ROSES: I'm also in awe of these authorities. So if it's required safety information that triggers these time-related events, and we've been looking at it as if all of the safety information is bad, so assume you had additional safety information that says with 99 percent accuracy that you can identify the people who have the adverse event.

Are they similarly subjected to this early release of information, even though that might change the competitiveness in the marketplace? Is that seen as advertising?

DR. WOODCOCK: Okay. That's another, you know, wrinkle on this, another subtlety, okay? What Dr. Roses has asked is you might have information that enhances the safety of a product through testing, and that -- I mean, we feel that you've probably -- the genetic data on genetic testing in warfarin ultimately will be shown to be of that nature, for example. How does that fit into this

scheme? And is it subject to early release, and so forth?

You know, I think everyone is still struggling with these paradigms, because they are all very new. And that's where I said, "Here you have new technology, say genomic data or others, that might identify who is at a specific risk." This is new territory, and the regulatory policy has to evolve in concert, which I think is your point.

So our job isn't -- we have to -- isn't just to absorb the new science. We have to do that, but then we have to make a regulatory policy that embraces it and is consistent with prior actions and is legal, and hopefully is in the best interest of patients, and so forth.

CHAIR SHINE: Other comments or questions? Larry?

DR. SASICH: Thank you. A question, and then a brief comment. Under Section 901, and the authority to require

clinical trials on safety issues, I kind of have trouble getting my arms around the ethics of conducting clinical trials for safety and what an informed consent document might look like in that situation.

And my comment is, and I hope I'm not offering up another unfunded mandate to the Food and Drug Administration, but in terms of numerous of a plethora of REMS programs that may be very divergent, I think the Canadian system to a limited extent has addressed this.

They have a special access program within Health Canada, and my brief -- the experience that I have with it was the withdrawal of Tasmar, which happened very, very quickly. This is a drug that patient -- a Parkinson's drug the patient shouldn't cold turkey on, and so this allowed a method for the government to approve the distribution of the drug.

The other was the Adderall

withdrawal, and the drug came off the market, the analyses were done, and it was subsequently reintroduced to the market as -- you know, would you have to go back to Congress to do something like that?

DR. WOODCOCK: No. I think those authorities are available now to the Food and Drug Administration. I will point out, though, that in our health care systems these things are more chaotic versus where you have a nationalized health care system, where, you know, the central edicts are able to be carried out, say in Canada by the provinces. They manage pharmaceutical access. That isn't the case in the U.S., and so because we have a different system we just have to run things differently here.

CHAIR SHINE: David?

DR. PARKINSON: Although one of the other questions I was going to ask you was, was there anything in the legislation to suggest that particular drugs or classes of

drugs could be confined to use by particular physician groups --

DR. WOODCOCK: Yes.

DR. PARKINSON: -- and yet you actually did describe them.

DR. WOODCOCK: Yes.

DR. PARKINSON: So that's interesting, and that's I think important, very important and very new within the chaos of what passes for health care systems in this country.

DR. WOODCOCK: Right. And that might be viewed by some as some inching down toward some reaching of FDA into the practice of medicine. Okay? But, in fact, we have restricted -- we have mandated -- we have made the manufacturers do it, though, in the past, and tell them, "You can only distribute to these guys," and that put kind of an excessive burden on the manufacturers who had to tell other physicians who might want the drug, "You can't have it," and it was the power of the

manufacturers.

But now it is within the statute to say, "This is a legitimate restriction that can be put by the Federal Government."

CHAIR SHINE: Dr. Woodcock, I presume that the effect of the Sentinel network could be to identify an issue which then became a subject of a clinical trial.

DR. WOODCOCK: Yes.

CHAIR SHINE: And you could then use that. You mentioned in the beginning of your talk $25 million in user fees and then a potential for $25 million for appropriations. Was that to cover the Sentinel trials? Or what does that cover?

DR. WOODCOCK: That was to -- well, it's hard for us -- I'm not a lawyer, so it's really hard for me to determine from the statute, but it had to do with drug safety, and I'm not sure which of the provisions it was actually intended to cover.

However, clearly, we are told to do

the network part, the pharmacovigilance in partnership, and we are -- you know, it would cost more than that if it --

CHAIR SHINE: Yes. I mean, one of the things that worries me about that is, in fact, the total cost, and some of the providers that you are asking to partner with you are already operating on very narrow margins.

DR. WOODCOCK: Right.

CHAIR SHINE: And it's not at all clear that -- what their motivation -- they would like to know in their population what the issues are. But there is going to be additional cost there.

DR. WOODCOCK: Yes. And what we're looking at, like many things we do under critical path, is consortia, public-private partnerships, because everyone stands to gain. Although these -- they would like to look, and they are looking in their own health care systems. What people would really like is

also to have their findings replicated in other settings or to find out, say, this setting finds out this other setting does a better job in managing this particular problem.

And that kind of sharing could be enabled by having a distributed network where you could do queries across --

CHAIR SHINE: Okay.

DR. WOODCOCK: -- multiple data sources. So there is something in it for everybody, or that's how we have to create it, so that there will be a common ground where it will be a win-win for a wide variety of people, because this could not be strictly a federal funded activity at the level of money that we have.

We also need money to -- we need more staff, because, as I think Andy said earlier, this is a new science, and there is going to have to be a research component of this.

CHAIR SHINE: Yes. I mean, this is -- the analytical part of this is going to be substantial.

DR. WOODCOCK: Yes.

CHAIR SHINE: It's not clear to me where the resources for that come from --

DR. WOODCOCK: Yes.

CHAIR SHINE: -- under these circumstances.

Yes, sir.

DR. SASICH: Yes. Just back to the clinical trials and the ethics of conducting.

DR. WOODCOCK: Oh, yes.

DR. SASICH: Thank you.

DR. WOODCOCK: Yes. We frequently do large safety studies for medical devices, and we -- not the government, but they are frequently done. They might be clinical trials, and it depends on the alternatives. We wouldn't take -- and also, the degree of certainty about whether or not the adverse event is actually related to the product.

If you believe that there is a signal, then you probably might not do a clinical trial to confirm it, if you actually believe there's a causal association. But in many situations you don't know, and, therefore, a clinical trial is the best way to rule it in or out. And for the purpose of ethics what you do is put in a Data Safety Monitoring Board and make sure as soon as you're certain then you would stop the trial.

CHAIR SHINE: And, finally, in your beginning presentation on critical path, you've talked about, if you will, the slowing pipeline of new agents, and so forth. Do you see any signs of that turning around in terms of applications to FDA?

DR. WOODCOCK: Not in terms of application -- of new drug applications. What we see is more INDs, so more people are trying. But, of course, we can't guarantee that there will be -- the success rate has gone down, so we don't know what will happen.

What we're seeing worldwide is a very low rate of applications.

CHAIR SHINE: Thank you very much, Dr. Woodcock.

In the few minutes before lunch, you will recall that the FDA actually did what I consider to be an outstanding job in analyzing the basis for the damage to pets associated with animal feeds that were brought in from China, which were attributable to melamine and a variety of metabolic products.

We had a very good presentation on that analysis, and asked that we get an update on the follow-up with regard to the lessons learned by that event and any additional information that we might receive about it. And Norris Alderson has agreed to do that.

Norris? Thank you.

DR. ALDERSON: Thank you, Board members.

I have to tell you, I really didn't volunteer for this.

(Laughter.)

You'll recall at the June meeting you heard from David Acheson, and unfortunately David is not available to be here today with you, but he did participate in preparation for this short briefing.

And we agreed, finally, that rather than parade up to five people during this time period up here we agreed that I would do this. And if you have questions, I've got support all throughout the room to help me, so here we go.

Just to bring you up to date today, what I really want to talk about is these three areas. What we've done in the area of methods development and validation, as you'll recall, at the June meeting we spent a lot of time talking about the resources and time that went into developing these methods very fast, so we could do a lot of analysis that took place.

I want to spend a few minutes

talking about where we are with the risk assessment that we briefed you on at the last meeting. David Hattan presented that information to you. And we've had a lot of discussion internally since the last meeting to talk about where do we go with the issues associated with melamine and its analogues in animal feeds, and we'll spend a few minutes on that.

But getting back to what we told you about at the last meeting, recall that in March of this year there was an unbelievable recall of pet food across the United States. It started out in just a few brands, but quickly expanded because of the efforts of a lot of folks in FDA developing methods and starting to look at the pet food that's out there in the marketplace.

We soon determined that that melamine it also could be in the feed for food-producing animals, which brought in a wholly -- a whole different set of

circumstances and risks we had to evaluate, and that was a big subject of the risk assessment.

That recall of that pet food is the largest emergency response that we have ever had in FDA. It was wide scope, many types of pet food, and then it expanded, as you will recall, into the food-producing animal feeds. Particularly in hogs and fish is where we identified some specific areas of concern.

Following that, we had to -- in concert with those feed methods, we had to develop methods for tissue as well. And you'll recall that we presented to you some tissue work that we had done based on some incurred residues and that we had developed into our CVM research facility, and we looked at a number of tissues in some animals we intentionally dosed with some material.

I have to point out, it's interesting -- and Allen Roses pointed it out during the briefing at the January meeting --

the significance at the time this Board was doing the science review, how this came across in terms of our ability to respond to this in the timeframe we were able to do it, and that happened just because we had the resources and the expertise in the agency, for without that you would not have been able to have the response that we had.

It's also important that, if you've paid attention in the newspapers in the last few days, Michigan State University, by its past history, has published a report of a survey that they conducted that based on this survey 300-plus dogs and animals were killed because of this pet food contamination.

So that gives you some idea of the issues associated with this. I don't have this right yet.

Okay. So what have we done in the methods development arena since the last meeting? ORA, as they always do, and you've got to understand that once a methods

development -- we always continue to refine that method to improve its efficiency, and that continues to be an effort of ORA and their labs, not only for just feeds but also for tissue.

In addition, NCTR has developed label standards for both melamine and cyanuric acid, labeling with both N-15 and C-13. The important thing to understand about this is those materials are not commercially available. Without NCTR, we would not have that capability to do the labeling -- to develop these label standards.

Now, the importance of these label standards is help us to continue to approve the efficiency of these methods, because with the label materials, as you go through the process of detecting these analogues and issue, you can determine with the label standards how efficient you are, particularly in abstraction, and that's where we lose a lot of these materials in the process. But with

this, we know how well we are doing.

You cannot say enough about that, of being able to have internal standards available where you can track what you're doing as you are analyzing the samples. It's also important because of the vast array of matrices. We have to look at these materials and just think of the different types of pet foods, feed for food-producing animals, and the tissues in the various foods that we're talking about. We're talking about fish, pork, beef, and poultry.

In the CVM area, they have continued their dosing in fish, particularly because we had some indications previously that the crystals were being formed there. And what CVM has continued to do, as well as providing these dose tissues to all of the laboratories involved, they began to study dosing with both melamine and cyanuric acid in four different fish species. They are doing serial sacrifice of those to look at the

depletion rate based on that dosing.

In addition to the residues, they are looking at renal crystal formation, and as of right now we really can't give you a summary of that information, where we are, because the analysis is not completed. But I can tell you they are seeing the crystals form in those fish that were dosed with both materials at the same time, as compared to no crystals when you dose singly.

What really got Renate Reimschuessel from CVM started with this was they got some cat crystals from other sources and began to look at those crystals for composition. That led us to do the work we are working on in fish today.

In the risk assessment arena, the information that we have internally within FDA, as well as the other work that is going on outside of FDA, we have seen nothing that would push us to change our risk assessment that we presented to you at the last meeting.

Now, there are some information needs which we talked about, and we are continuing to refine within the resources what we think our priorities should be in terms of additional information. I'll do more of that later, but, first, what is the mode of action of these materials as it relates to the kidney? And what are the species differences? And is there a bioaccumulation in edible tissue?

So, in summary, no new information change where we are from a safety perspective, but, yes, there are other things we need to do.

We wanted to put this slide up here, because I hope you've had the opportunity to look at our new food protection plan, because this material and this issue has a direct relationship, so I wanted to put just these points up there for consideration and think about melamine of how that fits in these particular points in terms of a food

protection plan.

Just briefly, prevention builds safety in this from the start. Intervention, a risk-based inspection, and testing, and how do we respond to that? Rapidly and with effective communication.

And then, in that we apply the food prevention -- food protection principles in this, focus on the risk. We think we need more information there, obviously, which we've talked about. Target the resources to optimize risk reduction, address both unintentional and deliberate contamination, and use science and modern technology systems to address these issues.

So where are we on next steps? If you'll recall, back in the risk assessment report that we presented to you, and you had an opportunity to look at back in June, there were two pages of additional things we would like to have, would help us. We've gone through a process internally since then to

look at, really, what's our priorities and which would help us the most.

This is where we come out. As I said earlier, any time we have an issue like this, the laboratories will continue always to refine the methodology, and that's certainly something in this particular instance we will always do.

We need to know, what's the dose threshold for these crystals to be formed? Is dosing sequence a pre-condition for eliciting renal toxicity? What's the effects of the other two analogues -- ammeline and ammelide?

Janet spent some time this morning talking about biomarkers for renal toxicity. Well, we need that here also.

Elimination of residues and crystals on termination of exposure. And then, with this information, what do we do with the risk assessment? Do we need to make some changes in it?

And so that's kind of the process

of where we are, Mr. Chairman, what has happened since the last meeting, and I would be excited if I didn't continue to recognize all of the great FDAers, particularly in our laboratories, who have contributed to being able to address this particular issue, particularly ORA, CFSAN, CVM, NCTR, and our FERN Laboratory partners.

Thank you, and I will call on these other people to address questions that I maybe not can answer.

CHAIR SHINE: Thank you very much.

Are there questions? A couple of things I wanted to ask. What is our current policy with regard to any of these animal foods coming in from China specifically at the present time?

DR. ALDERSON: I'll point to my CFSAN and ORA compadres over here to my right.

DR. BUCHANAN: In part, I'm going to have to call on Steve to talk about the rules associated with feed additives. But

these are not substitutes for protein when added to a product that is considered adulteration, if it's not appropriately approved as a human food. And as far as I know, it's not approved as a human food, so it would be an unregulated, unapproved food additive, if it was added to any protein concentrate that was being used directly for human food.

Now, I have to turn it over to Steve to talk about the restrictions for its use in animal feeds.

DR. SUNDLOF: In terms of what we're doing to prevent this from occurring, we have a -- we still continue to have an import alert, I believe, on all vegetable protein concentrates coming from China. And that means that no products that contain vegetable protein concentrates, including wheat gluten, corn gluten, rice protein concentrate, the products that were in the pet foods, can come into the United States unless they have been

properly tested and they can verify that they are free of these contaminants.

And so, as you know, we are also in the process of developing a food importation plan that will specifically address exporters and how we are going to verify in the future that foreign exporters are complying with the U.S. standards. So more to follow on that.

CHAIR SHINE: Thank you. The other question I had, Norris, was there was a real question, because these foods were being evaluated on their protein content, and this was not a legitimate protein content, so there was a question about where there was actually some fraud involved here, legally. And at the time there were investigations going on with regard to that. What has ever happened with that? Do we know? Have there been any --

DR. ALDERSON: I don't know.

CHAIR SHINE: Have there been any legal actions taken with regard to the behavior of any of the manufacturers here?

DR. ALDERSON: Carl or Steve, any of you?

DR. SUNDLOF: To my understanding, I don't know, there may be some criminal investigation that's going on within the Office of Criminal Investigation. We don't -- we're not privileged to that information.

I think the Chinese officials took some enforcement action against the people in China who actually produced this, but to my knowledge I am not aware that there is any criminal investigations going on, although it is entirely possible.

CHAIR SHINE: Yes, I'm not implying anything other than that the question was raised.

DR. SUNDLOF: I understand.

CHAIR SHINE: And I was curious as to whether there was a follow-up.

Members of the Board? Dr. Roses?

DR. ROSES: Yes, I was very impressed in June, as you said, and I'm still

very impressed. But in the interim period since June, I have had the opportunity to do some scenario testing for counterterrorism. And I think one of the things you had the right pieces in the right place at the right time for this particular response, but there is a growing body of knowledge concerning other things that could have tremendous effects on the human population.

Is the FDA a participant in some of these scenario testings, particularly those that are being done by the --

DR. ALDERSON: Ellen is not here today, but if she were here she would tell you that we participate regularly in these exercises looking at what-ifs. These go on regularly, as best I can tell you.

CHAIR SHINE: Anything else? If not -- John Thomas?

DR. THOMAS: Ken, as you'll remember, you sent me one of those initial risk evaluations on the melamine --

CHAIR SHINE: Right.

DR. THOMAS: -- and it goes back to biomarkers. Most of it was assessed on the basis of simply nitrogen, which was pretty non-descript and represented a cheap filler for this particular pet food.

CHAIR SHINE: Yes. And I -- again, I would emphasize that I was very grateful to members of the Science Board plus other consultants that we were able to get very rapid input on the risk assessment document that was created and give the agency some input.

Norris, thank you and your colleagues for the update.

Ladies and gentlemen, the Committee will adjourn to the -- there is a room in the restaurant for us to have lunch. We will reconvene promptly at 12:30. We have a lot of work to do this afternoon on the science report. I'd like you to keep this report in mind as we go forward with the science report.

We are recessed until 12:30.

(Whereupon, at 11:33 a.m., the proceedings in the foregoing matter recessed for lunch.)

P R O C E E D I N G S

(12:30 p.m.)

DR. SHINE: Good afternoon. Welcome back from lunch.

Before we have Gail Cassell present for the subcommittee, let me reiterate a couple of observations I made earlier this morning when the Commissioner was here.

I consider this project to be a tribute to both the wisdom and the courage of the Commissioner; the wisdom, because he was willing to allow the scientific programs of the FDA to be evaluated by a subcommittee of this board assisted by some 30 distinguished individuals from academia, industry, public policy, law, et cetera.

And he did so without any interference with that group, although the

group had staff support throughout the staff scheduled meetings, and scheduled conferences and so forth, but in no way interfered with either the conclusions, findings or recommendations of the subcommittee.

Secondly, it took courage because whenever you ask a group of individuals particularly loaded with academics to look at anything they can find things to criticize. But in the spirit of constructive criticism I was impressed at all these people who did their work pro bono, consultants all were uncompensated; that they cared about the FDA, they cared about its future, and they made recommendations and articulated findings that they believed were in the best long term interests of the institution.

Just before the break we heard a presentation on melamine. Melamine as you know is a substance whose breakdown products produced stones in the kidneys of animals, and killed several hundred dogs and cats. It was

a fact that the agency had significant scientific analytic capability that allowed them very rapidly to determine the basis for the illness. That capability allowed them to develop methods that could be used to measure the impact of feeding that material to livestock, hog and fish. And without the scientific capabilities that were available, this country would have potentially been in serious difficulty.

The scientific advisory board believes strongly that FDA must be a science based institution, although as you heard this morning and you'll hear again this afternoon, not all that science has to be carried out within the agency. Some of it must be, because it cannot develop the scientific basis for its regulatory function without a strong scientific infrastructure, and that that science must be available to meet its overall responsibilities when other agencies have a different set of responsibilities and so

forth.

The melamine presentation again demonstrates that within the agency there are some very good scientists who do very good work. And this board every year reviews nominations for awards for science achievement, and I'm very pleased the last several years when we evaluated this, it's been very hard to choose between the nominees, the science has been so good.

So the capability within the agency is very substantive, but as you'll hear, there are real limitations to it. The environment in which that takes place is being challenged. And if we're to meet the challenges of science going forward as the regulatory environment changes, there must also be changes in the way in which resources are provided.

And finally I would emphasize that some aspects of this report are in the control of the Commissioner, how the agency is

organized, and some of the other elements of it are clearly administrative activities.

But you will hear a great deal about resources, and resources are only partially in the control of the staff and the Commissioner. Resources are about the responsibilities of the Congress, of the administration, as well as of the private sector and with the establishment of a new foundation there may be opportunities for new public-private enterprises.

However the Science Board we believe can play an important long term role in overseeing the science activities within the agency and in helping to analyze and implement many of the recommendations in this report.

The subcommittee that was involved in this is chaired by Gail Cassell and included Allen Roses and Barbara McNeil. You will never fully understand the amount of time and effort that Gail Cassell has put into this

enterprise. I know because I participated in many, many, many conference calls. And that was a fraction of the work she did in putting this together. And we owe Gail enormous gratitude for the extraordinary leadership that she provided.

I also want to thank the other members of the subcommittee and the consultants, and we'll ask Gail to introduce the report. We will hear from a number of the consultants.

We will then entertain an action item by the board as part of our discussion of the report, in order to move the agenda forward.

Gail Cassell.

REPORT OF THE SUBCOMMITTEE ON SCIENCE AND TECHNOLOGY

OVERVIEW OF PROCESS, FINDINGS AND RECOMMENDATIONS

DR. CASSELL: Tim, I agree with everything that you have said. And in the

interests of time won't duplicate what you've just said, because there is nothing that I disagree with.

I first of all though would like to start out by again reiterating I think to the agency and to the Commissioner the gratitude and appreciation for all of their hard work as we went through this process, particularly Carlos Pena who was with us night and day, weekends, to provide information that was requested.

And then in addition I'll say a little bit more about the committee, because I think it's a very important point.

This afternoon in addition to my staff I requested several of the committee members to make a few comments as well. Those are the areas which were highlighted in the report, and I feel we need additional comment.

First of all, just to reiterate the charge to this science board, it was to appoint a subcommittee to assess whether

science and technology within the agency can support current, and more importantly perhaps, future core regulatory functions and decision making.

The subcommittee tasked specifically to identify scientific gaps. We've done that. We've identified those eight areas that we think are the highest priorities and must be addressed, in fact very quickly addressed because the onslaught of new products, technologies, devices is already upon us, so they have to be addressed.

And that goes for application of new technologies to foods as well as to medical products, and also manufacturing.

In addition we were to identify mechanisms for maximizing the effectiveness of science and technology capacity and priority setting. You will find in the report a lot of details about how we think the agency can maximize the great resources that they have in terms of human capital, the knowledge base

they have in regulatory science, and furthermore, the warehouses of data that they have that apply to biomedical research that are currently being unrealized, and you'll hear more about this in the presentations this afternoon.

And lastly to leverage the scientific capacity to invoke the public and private sectors. There is nobody working in the area today of science and research, U.S.. Competitiveness or preeminence in science, where we know that to be competitive and to succeed and to address the problems society faces overall that you can do this with one sector alone; you have to have public-private partnerships. In fact that's one of the major strengths of this country has been. I think we have a competitive edge, but we may be losing it very quickly in this regard.

One thing I want to emphasize that you will not see in the charge. Many will say this subcommittee has overstepped their

charge, overstepped their bounds. There is a reason for that, and I hope you all will agree.

The subcommittee was not asked to assess or make recommendations about resources. And specifically we were cautioned not to do this; that that was not our charge.

As you will see as we go through these presentations, there was absolutely no way to review one in the absence of the other, because the scientific gaps, the mechanisms for maximizing and leveraging, cannot take place without adequate resources.

And furthermore, if in fact there are not adequate resources as you will see, this will greatly compromise a lot of the dreams that we all have, and expectations that we have of the agency.

I want to emphasize the uniqueness of this review. Today we have unprecedented scientific advances that will allow us to reduce regulatory uncertainty. Never before

in history have we had such tools.

We will not be able to take advantage of those tools without the appropriate resources, without the appropriately trained personnel and scientists.

Increasingly complex product reviews based on advances, as well as globalization. Innovation is coming from around the world, not just from the United States anymore; from within our own borders.

There is increased scrutiny of agency by all stakeholders; I need not expand on that, we all greatly appreciate that.

An unprecedented opportunities, as I've already said, to leverage with partners. There is a decline in funding in real dollars. Peter Hutt will address this toward the end of our presentation this afternoon.

One thing that I want you all to appreciate, this is only the second time in the history of an agency that has been in

existence for over a century that a committee has actually been asked to look at the agency as a whole: what are the gaps? How can we maximize what we are doing? Only the second time. But as far as we can tell from looking at as many documents as we could get our hands on, only the second time.

This is very significant, because you can review one program at a time, one center at a time, and not be concerned because you can perhaps feel that you can address those concerns.

When in fact you look at the entire agency as a whole collectively, and you keep hearing recurring themes, as I will expand upon in just a minute, this is what makes you in fact concerned, and this is one reason that we have been so brutal if you will in this report. Because we were looking at the agency collectively for the second time in over a half-century.

It's unique because it is the 100th

anniversary actually we started during the year of the 100th anniversary in 2006. This is a very critical time for FDA in its history. And it's a very critical time for society in general.

We can actually accept the fact that they are greatly under resourced, and I would say, as some of our committee members have said, limping along. Or we can restore it to the gold standard that it has been worldwide.

We are rapidly losing the ability to set standards, and we will be following the standards set by other countries and other regulatory agencies if we don't act and act now.

Sorry to be on the soapbox. Just one more word about this committee. The composition I would argue also is unique. When you review, because of a lot of issues surrounding advisory bodies, many previous committees, you will see a definite imbalance

of individuals either from industry or academia or government.

We went to great lengths in selecting this committee to identify the very best people in the public sector, the private sector, academia and government by the way. And we think I don't think, I know we have the very best.

We had 33 people that were more engaged than any other committee I've ever worked on. I co-chaired the congressionall8y mandated review of the National Institutes of Health over a decade ago. I was also on the committee that wrote the Gathering Storm report that was also requested by Congress. We had a lot of really good people.

But I'm telling you, nobody, no committee, has ever worked better together, and harder, in terms of providing input and assessment than these 33 individuals.

I think that is a testament, number one, to two things: one, how much people value

the agency, their appreciation for the impact this agency has on all of use; and lastly, and importantly, the concern that each of the 33 members has about the future of the agency unless we address the deficiencies that we have identified in this process.

What was the process? First of all and importantly, we asked FDA to tell us each center, what do you think your major gaps and challenges are? You have two appendices in the report, Appendices L and M, that go well over 200 pages, where they have very thoughtfully put together center by center what they see as their greatest challenges, and not only that, but maybe for the first time in history, each of those are linked back in Appendix L to their regulatory application.

I would argue in fact if you take that, and the fact that we divided our committee into subgroups looking at every center, three cross-cutting programs genomics, surveillance biostatistics, and

information technology then in fact this may be the first time in history, at any given point in history, you actually have a blueprint for moving forward, because you know, based on both internal assessment and external assessment where the gaps are, what the needs are; again, a uniqueness I think with regards to this particular group.

The other thing is that we did not have time to nor did we have the intent to review individual scientists nor individual laboratories. I think that is an important point for the Science Board to consider in looking toward the future.

The structure of the report: it's important that you realize that while we had these working groups looking at every center, all of those reports, including very specific findings and recommendations, are not in the report. They're in Appendices D through K, in detail.

But what is in the report are those

issues that were identified as common, recurring themes, as far as what the gaps were, and that they were cross-cutting issues.

Detailed reports, as I've already said, are for each of the centers, are in these three cross-cutting programs, are in the appendices.

I'm not going to try to walk through all of the recommendations nor the findings, because those are spelled out in the report. I've tried to do that a little bit of the slide handout that I gave you, but I won't take time, to try to conserve time.

But you should realize that the one resounding conclusion that we reached very early on is that science at the FDA is in a precarious position. The agency suffers from serious scientific deficiencies, and is not positioned to meet current or emerging regulatory responsibilities.

And the bottom line is, demands of FDA have soared; resources have not. The

reasons demands have soared, there's been an extraordinary advance of scientific discoveries. I mentioned the complexity, the globalization issues, and also emerging emergence of challenging safety issues just because we are getting better at the science. We understand the complexity, the different reactions, the genomic effect as you'll heart from Tom Caskey this afternoon, of product development.

The impact of these deficiencies are profound, because what is underappreciated by the public and the policymakers is that science is at the heart of every decision made by FDA. If we don't get the science right, all is for naught.

And that ranges all the way from pre-product review all the way to manufacturing, and years out as we monitor the surveillance of the performance as far as safety and efficacy of new products.

Very important that you keep that

in mind, and I would emphasize that from its founding the FDA was charged with doing research basically as it related to food safety, and by the way, something that you never hear, three of the six centers within FDA have research in their title: CDER, CBER, NCTR. Keep that in mind.

As Dr, Shine has said, not all of it is in fact laboratory based, nor should it be. It is not a basic science research agency. We never wanted to be. But there absolutely are very critical important areas of research that have to be done and can only be done by the agency, and if it's not done in-house, they're the ones that identify those needs. They need to have the resources and the mechanisms to allow them to get that work done.

Just to mention the fact that I the handout of the slides I talk about the breadth of the responsibilities of FDA, and would remind you that science is at the heart of all

those Janet will recognize them, because I borrowed those slides from a presentation she gave us early on.

What you may not appreciate is that in 2006 the FDA was responsible for monitoring over 300,000 sites around the world. This was on every continent, and in over 100 countries. Imagine that.

So FDA, it's not hard to imagine if you really look at the breadth of their responsibilities, touches lives, health and well-being of all Americans, I would argue much more so than any other federal agency or entity; it is absolutely integral not only to our health and safety but national economy and also security. And we won't get into that, but we know we could talk all day about that.

It regulates this agency regulates a trillion dollars in consumer products a trillion dollars in consumer products, or in other words, 25 cents of every dollar that every American spends annually in this

country.

But listen up, while in fact they regulate a trillion dollars, their budget, appropriate budget, is only $1.6 billion. It doesn't take a lot I think to figure that versus the large number of oversight responsibilities that we've just referred to to realize it's not enough.

Each American only pays today 1-1/2 cents a day for FDA to regulate over 80 percent of the food they eat, and all of the medical products in fact they depend on for life, essentially.

I'm not going to go over a lot of the findings. But just to hit some high points that you will hear about later. And that is, dealing with the scientific organization and structure within the FDA, and also with respect to new science and how we think in fact FDA needs to position itself with respect to that.

You will hear also about one of the

other major findings that deal with food safety, and the fact that we now have, due to constrained resources, fire-fighting regulatory posture instead of pursuing a culture that is pro-active regulatory science which you absolutely have to have to protect the public's health; otherwise you are always playing catch-up.

There are, as Dr. Shine referred to, a lot of positive trends at FDA. And you cannot misjudge those. Because in fact with very few resources FDA has taken some very positive steps over the last few years.

One, the Critical Path Initiative, which you heard from from Dr. Woodcock this morning. But you will see in the report, it's a great idea, but we need more resources if in fact that great idea will ever in fact be realized, those ideas, ever realized, which are crucial.

Next there is a consolidation of laboratories and personnel at White Oak

facility. It's wonderful, but will only realize its full potential if it's fully resourced.

The establishment of the Reagan-Udall Foundation is great, but unless I'm wrong, Janet, what I have understood is that only $1.5 million of FDA monies can be put towards this foundation. That's hardly enough for operating expenses, much less to really stimulate, and be a full partner in terms of conducting work in this new and valuable foundation.

There has been the appointment of a deputy commissioner for the first time referred to as chief medical officer. This is great. The committee would have liked to have seen that title be chief medical officer and scientific officer to acknowledge the role of science. And by the way we think that is a huge job for any one person, and ideally what you'd like to see is not only a chief medical officer, but also a chief scientific I mean,

sorry, a chief scientific officer and a deputy commissioner for science, and a deputy commissioner for medicine.

And then lastly, Ken, I think that your comment about having asked this committee, the board, to review the science and technology is a very positive step. One of the recommendations you will see in fact is that some centers and programs have not undergone review, just like the agency as a whole, very rarely. We think this is a big mistake. A lot of good things can come from constant and consistent external peer review. Not only do you identify gaps on the spot, but you also educate others from the outside in terms of what the real challenges and needs are. They can become the strongest advocates for making changes.

I think then that the other thing you will hear about this afternoon are some of the other recommendations that we referred to. And I won't say more, other than the fact

that Ken, we did not really, and members of the science board, I think you can appreciate that we really didn't have time to do an in depth review of the Office of Regulatory Affairs which obviously is dependent on good science, and having outstanding scientific personnel.

We think there needs to be a closer look at the National Center for Toxicological Research as a valued asset, but how can we maximize it even more?

And then lastly, we agree with you, Ken, the Science Board should play a very active role going forward in terms of timely and effective implementation of the recommendations of the subcommittee; but also to see that we have in place good mechanisms for constant and consistent and rigorous peer review programs.

With regards to the workforce issues, I applaud Dr. Von Eschenbach this morning. I heard that he announced a very

exciting initiative for an addition of, is it 2,000 new fellows over the next two years. This is exactly what you would hope would happen, but I would point out, I think in all fairness to Dr. Eschenbach, this won't happen unless we have more resources.

Did you know that currently, in fact in five of the major centers, that we have under 100 total fellows and visiting scientists working in the agency. Some, like the Center for Veterinary Medicine, don't even have the resources to have a single fellow, or a single visiting scientist.

Think about that. Think about the value we all know of bringing young people in, training the next generation in regulatory science, having visiting scientists on the cutting edge, right to work beside those in the agency. Think of the opportunities lost by not having enough resources to have those programs.

Lastly, and more importantly, what

we consider to be possibly the very weakest link is the information technology infrastructure here at the FDA. This is something that absolutely needs immediate attention. And Dr. Dale Nordenberg who is on our IT working group will address that.

I'd like to introduce now the next speaker who is Eve Slater. Eve has a very impressive background in that she was senior vice president for regulatory for Merck for years, not only for vaccines but also medicines. Under her watch there was not a single black box, which is remarkable I think given what we know.

In addition she also took time out to recently be a public servant, and served as assistant secretary of health, so she knows the government side. And now she is senior vice president of public affairs at Pfizer, and has agreed to graciously agreed to come this afternoon.

Thank you.

HUMAN CAPITAL AND SCIENTIFIC INFRASTRUCTURE

DR. SLATER: I should note that actually when I agreed to serve on this committee I was not employed by the industry. Only joined relatively recently again.

Thank you very much, all of you, for your attention to this topic. It comes as no surprise to any of us that the FDA is at a crisis of confidence as we speak.

Media and congressional criticisms seem even more numerous than ever. And while the FDA Amendments Act passed in September creates unprecedented opportunity, the operating environment is unlikely to improve unless further actions are taken, which was in part the attempt of this committee.

By now you are familiar with the outline of the report, and Gail has had the opportunity to review with you in broad terms the budgetary and organizational issues that we discussed as a consequence of our extensive deliberations.

Please be assured that our recommendations are being made in the spirit of deep respect for this agency and its contributions, and with recognition of the dedicated service to public health that is delivered 24/7 by this agency.

The urgency of our advisory is simply predicated upon the fact that we see signs of an increasingly chaotic environment descending upon you, and we hope to rally support for your mission.

My charge is to focus on the human capital and scientific infrastructure. So even as far back as 2005, when I wrote in the New England Journal a sounding board piece entitled, Today's FDA, I called for urgent attention to infrastructure.

To simplify our rhetoric, your job is to get the right drug, device, food, so forth, to the right person or pet or whatever at the right time.

And there is a misperception even

among those who commented on this report over the weekend that somehow strengthening the FDA and the science of the FDA serves the pharmaceutical industry. This is a very naive notion.

As I stated back in `05, the need is for equipoise. That is in any negotiation, whether it be to allow a phase one trial to proceed, to approve a device, whether it be a labeling change or approval for a DTC ad, the scientific expertise of the regulatory must be on a par with that of the industry negotiator.

Without this the playing field could become tilted.

So within the three pillars identified in our report the research agenda for regulatory science, the staff that supports that agenda, and the infrastructure that supports the staff especially IT there is urgent need for infusion of money and the personnel capable of creating the state-of-the-art center for regulatory science required

by a society that relies on you to ensure their safety, safety and efficacy of products that they use, 25 cents out of every dollar.

Human capital and infrastructure are key; you will hear more about the details of our report on information technology in a moment, and also on the details of the specific scientific initiatives that were discussed.

Cathy also will talk very much about food safety in a moment.

But I will focus on a concept that I believe actually supersedes each of these important considerations, and that's the notion of a field of regulatory science.

The FDA has at its disposal a wealth of experience and data. To support the science, and it's an emerging science, of risk-benefit analysis. And this is really where we feel that the scientific expertise of the agency needs to be encouraged, and needs to be infused with vision, resources,

personnel, manpower and remain on the cutting edge.

We hear about personal medicine all the time. Right medicine, right person, right time. And this is of course the key ingredient of the critical path initiative, which hopefully will be enriched by the Reagan-Udall Foundation, and the creation of the Incubator for Innovation in Regulatory and Informational Science, the IIRIS, as noted in Section 3.1.2 of our report.

Development of tools to translate the products of innovation have never been better. But to do them justice you need an infrastructure and human capital inspired by the vision and not handicapped by resource limitations of its current magnitude.

Beyond IT, you need an experienced portfolio manager to guide the projects along. Beyond vision you need scientists trained not only in systems biology but also in newer biostatistical methods, such as data mining

and so forth.

Beyond reviewers conversant in regenerative medicine, you need experts in the emerging disciplines of risk-benefit analysis and importantly risk communication.

Gale asked me to say a few words regarding drug safety, and we are all very familiar with recent reports by IOM, GAO, HHS, and amplified by numerous academic analyses of several recent drug safety crises.

Title IX of FDAAA fortunately has provided a path forward, provided that the promised funding materializes, and that proper planning for implementation of these recommendations takes place, takes place with manpower that has the time and the luxury of time to be able to plan for this important aspect of FDA responsibility.

We devoted several sections, and in fact Sections 3.1.1 through 4 to recommendations regarding human capital. We noted the efficient recruitment and retention;

the need to develop more career ladders; to encourage fellowships; encourage intra- and extramural training, resourcing from your sister agencies.

It is critical that you institute performance metrics. And fortunately, this is perhaps one of the few recommendations we were making that will not require too much more in the way of appropriation.

We have spent quite a bit of time in the report focusing on the need to establish as Gale said an office of chief scientist for FDA, reporting to the deputy commissioner of medical and hopefully scientific affairs, as the name should change, or perhaps even as a separate deputy commissioner level.

Perhaps we could put up the slide that you kindly made for me that basically outlines this structure. Thank you. I don't know if anyone can see it, but it's in your handouts; it's in the handout on your lap.

But basically the chief scientific office is on the far left as I see it.

Now reporting in to this chief scientific officer and let me emphasize, this chief scientific officer should not be an officer in name only. The chief scientific officer must have ample budgetary responsibility to be able to follow through on his or her recommendations.

Reporting to this person, this person obviously needs input, and therefore we are recommending that there be deputy directors for each of the centers responsible for monitoring the science for which the center is responsible.

These individuals as well should have budgetary discretion and also play a role in the developing of scientific priorities, appointment of fellows, and the development of extramural collaborations.

And these individuals can and should be enabled by outside boards, and

informed by outside boards at the center level, and oversight of course can be provided by the Science Board itself.

Then further on the far right-hand box we have recommended the creation of a director of extramural collaborations and training in Section 3.1.4, and then as you'll see also the establishment of the IIRIS, the Incubator for Innovation and Regulatory and Information Science wherein ideas can be generated, and this group can perhaps have some form of informal or dotted line type of relationship to the Reagan-Udall Foundation as that opportunity evolves.

So the vision of a culture of regulatory science enabled by an environment where personnel and infrastructure support that mission will lead to an FDA that is confident in its service to public health. And that of course is that we and all of us sincerely desire for the FDA, and certainly what the American public needs and deserves.

So thank you very much. I guess there will be questions afterwards.

DR. CASSELL: Dr. Slater agreed to come and say these important words with us this afternoon even though her son will be performing tonight beginning at 6:00 o'clock at Carnegie Hall. And this is a very young son. But I just wanted to share that with you, to let you know just how committed this committee is and has been, and really have not denied any of my current requests.

So thank you, and we will excuse you to be sure that you get there on time.

Bottom line is, FDA today, the total number of personnel through appropriated funds is the same as it was 15 years ago. Stop and think about that in the face of the expanding responsibilities we've talked about, and you'll hear more about from Peter Hutt.

And lastly, you often hear people at the agency say, ah, we can't deal with another advisory body. We know you have many

advisory bodies.

I would wager, however, that this board of external scientific counselors that we are asking you to establish will be one of the most important groups of external advisers that the history of the agency will have.

Last week I gave a keynote address at NIH, and I was actually presented with a bound copy of the Cassell-Marks Report of the Intramural Program of NIH, and I can only tell you, this was well over a decade, the report was released. But the point was, they were talking about what an impact these changes in terms of a peer review, in the rigor of the training programs, has had on the impact of the agency.

So I just couldn't resist sharing that. I apologize, Ken.

Next, I've asked Cathy Woteki to tell you a little bit about our strong recommendations as it relates to food safety.

Cathy is uniquely qualified to do

this, having served as undersecretary of agriculture. By the way also at the Institute of Medicine, and by the way, as dean of the Veterinary School at the University I'm sorry, dean of the Ag school, that's even bigger and better sorry, Lonnie but now is actually in the private sector.

So I can think of no one better to address these issues, having served in all sectors. So Cathy, thank you.

SCIENTIFIC GAPS: CAPABILITY AND CAPACITY

FOOD SAFETY: A STATE OF CRISIS

DR. WOTEKI: Thank you. Didn't want to take on a degree I hadn't earned.

I want to turn your attention now to what the committee where are we going here there we go to what the committee considered after our long deliberations to be the two orphan centers within the Food & Drug Administration.

And those are the Center for Veterinary Medicine and the Center for Food

Safety and Applied Nutrition.

The reason that we came to that conclusion was the neglect and erosion of their resource needs over really what amounts to being decades. And that erosion now means that they can't really address anything beyond the top priorities that are on their plates, and also, that major issues of public health concern are not being addressed, and particularly the two areas that we were most concerned about were cosmetic safety and nutrition.

Now having said that the committee also recognized, and it's written in our report, that it's really through the extraordinary efforts of the staff in these two very important centers that have focused the resources that they have against those top priorities, and have managed so well in so many different crises that they have faced, that they have been able to carry on as they have to address the major public health

concerns.

But our conclusion is that that they are now so frayed, and so stretched, that this is a major issue for the entire agency to face.

The context of our review I think is very important. We started our work during the winter of 2007, so earlier this year, and we worked through the late spring, in collecting and beginning the analysis of information that we obtained from the agency as well as from a number of different organizations and individuals that we consulted with.

And during this period of time there were a cascading set of food product recalls that were going on, both in the human food as well as in the pet food area, involving E. Coli 0157h7 in fresh spinach; salmonella in peanut butter; and the melamine incident that we heard about earlier this morning, which was extraordinary. It resulted

in more inquiries to the agency, over triple the number that they get on an annual basis.

So at the same time, the Center for Veterinary Medicine, the center that was at the center of responding to this melamine contamination, only has two full-time people who are working on pet food issues.

So it required drawing on resources not only within CVM, but very broadly within the other areas within FDA.

So our primary finding in the committee's report as it relates to food safety is that FDA does not have the capacity now to assure the safety of food for the nation. The basic functions like inspection, enforcement and rulemaking, are severely eroded.

And as examples of this there's been a 78 percent reduction in inspections in these areas over 35 years. So again we are not talking about recently; we're talking about over a period of decades.

Food establishments are inspected on average about once every ten years. The CVM workforce is at 375 FTEs, or only about 4 percent of the total within FDA, but yet they face unique and really diverse responsibilities as it relates to the many, many species that they must address, as well as maintaining a human health orientation.

In CFSAN just in the last five years the workforce has declined from 950 FTE to 771 FTE. Cosmetic safety only has a total of 20 FTE, to address this huge area.

And lastly the CFSAN no longer generates the science that it needs to undergird its responsibilities in human nutrition.

Now why has this happened? Well, on the one hand there has been a dramatic increase as well as a diversification of the responsibilities that these two centers face. Again, just in the last five years there have been additional legislative responsibilities

that relate to food contact surfaces, bioterrorism response, food allergen labeling, transfat labeling, egg safety and pandemic flu planning as well as minor use and minor species health in the veterinary medicine area.

Both centers are facing an increased complexity in the tasks that they have to undertake; increased scientific demands as not only the evolving scientific base, but the consideration that has to be given to that in any of its decision making; compounded then by inadequate resources.

Now in one way we should have anticipated that we would have ended up in the situation that we are today because back in 1991 a report of an advisory committee on the Food & Drug Administration was delivered to the secretary of what was then called Health and Human Services. And that report said there are deep concerns about the viability of the food programs, and the lack of agency

priority for food issues; decline in resources and program initiatives during the past 10 to 15 years indicate a lack of agency management attention and interest in this area, although public interest in and concern for an effective food program remains high.

Now the food regulatory environment is very complex. FDA does not have the only responsibilities in this area. They do have major responsibilities.

But they're divided within the organization itself. And they are also shared with the U.S. Department of Agriculture, the Department of Homeland Security, the Centers for Disease Control and Prevention, and also most importantly, state health and agricultural agencies.

So it's not only a coordination issue among national agencies, but also with respect to state agencies that FDA has to address. And with respect to the research base it has to access, most of that is being

sponsored by either the National Institutes of Health or two agencies within the Department of Agriculture.

So it's highly complex regulatory and science environment in which they operate.

I'd like to now turn to our specific recommendations as they relate to CVM and to CFSAN. And first up, I'd like to address CVM.

The report, the committee, endorses the agency's high science priority areas, and these are four.

First of all methods to identify residues as well as emerging infectious diseases. The anti-microbial resistance monitoring function, the science as well as the informatics required for the NARMS system.

Biotechnology as it relates to genetic engineering, cloning, and use of phages of bipharma.

And fourthly, new technologies in drug manufacturing and delivery, as they

particularly relate to nanotech, genetics, biomarkers, new approaches to categorizing microbial resistance.

The key stressors that CVM are facing are a convergence of a massive data volume and complexity with newly developed products from the Omex revolution.

Unique databases with respect to the number of species and the diversity of species and endpoints, as well as human health, and that is compounded by the under-staffing problem, and vacancies in key scientific positions, along with lack of funding.

Our recommendations with respect to CVM were to bolster the in-house scientific capabilities in emerging areas that are relevant to veterinary medicine, bolstering the IT capability and integrating within FDA with CVM partners, and Dr. Nordenberg is going to talk about these issues more later.

And then lastly to foster

integration with cutting edge science activities, not only across FDA, but also with the external partners and expanding the FDA fellows program.

With respect to the Center for Food Safety and Applied Nutrition, the committee also endorses seven of the agency's top priorities in this area.

The food production sciences particularly focusing on risk mitigation at the source. Consumer understanding of nutrition and food safety information, so that labeling can be more informative, and we hope that people will be able to act on that labeling as well.

Implementing the Food Allergen Labeling and Consumer Protection Act in effective interventions; detection of food borne viruses; and the development of prevention and intervention techniques to prevent food borne viral diseases.

Safety of cosmetics, and lastly,

adverse event reporting and analyses.

The key stressors that CFSAN are facing are, again, lack of resources; the decline that I've already mentioned; new mandates, as well as the fact that CFSAN has had to eliminate its extramural research programs; globalization of the food supply; the development and implementation of a wide variety of new food processing technologies; the emergence of new threats to public health; the ongoing ever-present emergency response that CFSAN faces; outmoded IT systems as well as laboratory instrumentation; and the fact that they are able only to address the highest priorities.

Our recommendations for CFSAN are that additional resources be provided to attract, retain, and to leverage the scientific expertise and regulatory research in the seven priority areas that I've already mentioned.

Again, this is not a complaint

about the way the agency is currently working. Rather, we feel very strongly that the staff within CFSAN is doing a commendable job in setting priorities and developing innovative ways to leverage what little that they do have.

And secondly, to provide leverage for them to interact in a collaborative way with research agencies so that they can get the research focus onto this regulatory science that they need created.

Priorities are immediately to correct the lack of support for staff and infrastructure, and that means funding, and to invest in the 21st century regulatory science that could anticipate future food safety issues and develop a cadre of professionals capable of applying the new science to emerging challenges.

In addition we strongly recommend that they be provided with resources to allow them to leverage research programs sponsored

by sister organizations, and that this be done in conjunction with the chief scientific officer that Eve just described to you.

And while building the veterinary and food safety capacity we want to remind that we not neglect the other two very important areas within these two very important centers that relate to human nutrition and cosmetics. These are big industries, and they are not being addressed.

Thank you.

DR. CASSELL: Our next presentation will be given by Dr. Tom Caskey. Member of the National Academy of Sciences, a terrific academician. By the way also having gone to Merck rather early on in his career to lead an effort in genomics, and now back as head of one of Texas' premier institutions as it relates to genomics.

And he tell us where we are at FDA with respect to genomics, and where he thinks we need to be.

Tom.

GENOMICS: IMPACT, CURRENT AND FUTURE CHALLENGES, AND OPPORTUNITIES

DR. CASKEY: I see my responsibility to support a vision and accelerate commitment.

My opinion is that the genome initiative is probably the transforming event of a century for advancement in medicine. We are only in year seven. So that's a strong statement.

What I'd like to do is highlight on this slide one, a dream, and two transforming events.

In 1990 when the commitment was made by a strong group to proceed with the genome project, no sequencing instruments available. Bioinformatics couldn't handle it. And the molecular biology was not available to do it. Truly a dream state.

We look back on it now, the dream was fulfilled, the promise of the science achieved.

The two transforming events, though, for others that I want to point out, and let's go to item three. Upon the discovery of the high frequency of polymorphic triplets in tetramers, it was a ah-hah moment for the forensic science community. Because they knew simple PCR automated machines, informatics, would free the innocent, and convict the bad guys.

One billion dollars committed to it; out of that has come tremendous programs with the UK national office, and of course the FBI, and also CSI, I must say. You know we probably supported CSI.

(Laughter)

The last one, which I think for me is an ah-hah moment is the individual genome sequence. The breakthroughs that have taken place in the last two years reporting complete genome sequences on individuals have been done with old devices. These devices have the capacity of only being able to turn out

gigabytes of data in a day.

The new I'm sorry, terabytes gigabytes. I get this mixed up. And the new instruments have the capacity to move to terabyte output.

Now if you have a vision for the FDA to have personalized medicine, to correct drugs and avoid the toxicities, you couldn't ask for a better situation to be dealing with for an ah-hah moment with new technology.

I won't go over the points on this slide, but just again to highlight a couple. On item four, clinical trial sectoring. All of us now accept this is by far and away the best way to go. It gives us a limited population of patients to study. We can test the utility of our drug against that target for ideally selected patients, so HER2 chronic myelogenous leukemia, epidermal growth factor strategies, have all been developed with that strategy.

It works. It'll be applied more

and more. It's the proper way to go.

We're going to come back to a new problem created by this strategy.

Item #5: biomarker usage, highlighted in earlier talks today. Janet certainly made very good points on that.

I remember this from our Merck days when PCR enabled us to measure the viral titers . We moved very rapidly once we had that tool in hand.

And I'd like to go to item #6. We've already commented on drug toxicity, and the success that's been enjoyed by the discoveries related to the launching of abacavir. And I'd like to just make the point that four and six are linked. As we go to smaller and smaller populations of patients to demonstrate the utility of a drug, the cause of sectoring of the trial group, we expose the drug to smaller numbers of people.

So upon launch we expose the drug now to large numbers of people. So the safety

factor that we had, by the targeted population, we do not have now because it's a small group.

So it is critical that the FDA and the scientists in the room take on the objective of post-launch safety, as we end up with greater and greater efficiency to approve the drug on target.

Now the FDA has done a remarkable job in my opinion in trying to move on the initiatives of genome science. We have already talked extensively about the critical path initiative. Absolutely the right direction to move in. We've talked about trying to herd the cats by bringing in the pharmaceutical industries to share data, with the Expression Database sharing. Kudos to FDA in achieving that.

And we've already heard earlier today about the FDA outsourcing to highly technical companies that do high throughput DNA sequencing in the area of infectious

disease. Right decision; right move.

And then the formation of a genomics working group, absolutely the right thing to do.

So the FDA has been moving effectively in these areas.

Now what are the points that we could make based upon the review? The Critical Path Initiative in my opinion and in the opinion of most in this room would be, it was visionary. It was underpowered, if you take a look at the examples used by the FBI, and examples used by NIH.

So the right idea, but underpowered in commitment.

Number two, genomics leadership is small. It's been predominantly an add-on responsibility for people who give a lot of time already to projects within FDA. And it's been handled somewhat in an ad hoc manner.

More recently an ad hoc manner by enthusiastic scientists, I might add these

people gave extra time to make this work.

Number three, a focused genome leadership has only really been identified and enhanced, and I still feel and the committee feels, inadequately funded.

And then the technical base now is somewhat limited because they are using instruments that are coming off the shelf as opposed to being involved with investigators that are providing state of the art new instrumentation, such as the high throughput sequencing that I've just mentioned.

So let me go through quickly the recommendations. One, it's necessary to formalize organization of the genomics program. I think the best example that I would give of the FDA moving in that direction would be the data sharing on the Expression Databases.

There is more in the report. Please take a look at it.

Recommendation #2: mechanisms for

recruitment, training, retention, high quality staff. This is definitely an area for immense improvement, an enhancement of the FDA's capacity. And it really links in my opinion, as you move on these new technologies, both genome science and informatics.

I'm a genome scientist. I'm not an informatics person. But my machines won't work unless I have informatics. And informatics will not work unless they have my machines.

And so it's absolutely synergistic that these two be enhanced. The leadership training as we've already mentioned of bringing in young people, 2,000 fellows into the FDA is absolutely an outstanding announcement that we've heard this morning. We all know that you have to have experienced trainers though to make those fellowships work well; and you've got to have the funding to fund them.

So while the vision is good, the

details need to be worked out and carefully developed. It's the right idea.

Recommendation #3: The committee strongly recommends increased collaboration with academic centers of excellence and other agencies in the private sector.

And I know from my experience in the commercial world, you do better with these collaborations when you come with an open checkbook. To go and set up a collaboration in which you cannot write a check, you hear very small and weak responses.

So the mechanism that is already in place, the CRADAs, which have been used very successfully by FDA, offers an opportunity to expand, the opportunity for FDA to develop its own directions and research programs working with expert centers and working with biotech companies that can give them the data they need for advancing their mission.

And I would give you one example. There are many people working in the area of

preclinical safety testing. How do you validate preclinical safety testing for the outcome? Well, a way to do that is to take the approved drugs that have come through FDA; study those outcomes against the preclinical safety mechanisms.

How many companies do you know of that would take on that particular challenge? I say that FDA can do that with CRADAs and can do it with the right selected companies, and our committee feels that way.

Recommendation #4: private-public initiatives. You have to develop of course a win-win situation, so let's face the facts here. You got leading health care corporations that have the patience, they have the electronic records, they have the outcomes. If we can improve the care of those patients in both the outcomes of their health care and the efficiency of cost of drugs, by selecting the right drugs for the right patient, we've got a perfect win-win situation

for FDA to be interacting with the health care provider.

The other one I would point at at a more basic level, you've got very narrowly focused biotech companies that have the ideas, which need to have validation through FDA.

Recommendation 5: this is all about critical mass. If you don't have the scientists in house that think and breathe and discuss genome science, nucleic acid, proteomics, mass spec, you name it, then you don't get the original idea.

Let me just remind you of a couple of discoveries that we all use daily. DNA chips, sequencing, pathway analysis, RNAi. I think the largest number of scientists that made those contributions in those research groups was five. There were five people in the sequencing group.

Now did five people brilliantly come up with those ideas? No, they didn't come up with it alone; they came up with it in

the environment they probably cannot even recall how the synapses occurred to lead to those developments.

So the critical mass is needed for the FDA to have a prepared mind.

And then the last point that not I will make but that the committee made was in order for genome core groups to function we've got to have an information technology infrastructure. And I've already made the point: I don't know of many information systems that would be able at the present time to handle the output that we currently can generate in DNA, DNA sequencing, probably new pathway analysis systems. So in order for us to make use of this new technology, we've got to have it interpreted by electronic methods.

Thank you.

DR. CASSELL: Thank you very much, Tom.

Our next presenter, to give you another indication of the commitment of the

committee, is Dr. Garret Fitzgerald, who's joining us from Rome by way of phone.

Garret also has a unique area of expertise in translational research, and a strong commitment to training the next generation in regulatory science, but is here this afternoon with us by phone to emphasize the importance of the FDA having in place mechanisms whereby they can scan the environment, identify new areas of emerging science that they will be dealing with, so in fact they can actually be prepared and not constantly be playing catch up. The science is too complex to depend on being able to catch up after the fact, after you are already receiving products for review, or not using the most up to date technologies.

Garret, thank you very much for going to so much trouble to be with us.

DR. FITZGERALD: Thank you, Gail.

DR. CASSELL: And I'm sure you haven't seen the two slides that I pulled

together for you to talk from. They are from the key messages that you had sent me over the weekend. So thank you very much.

DR. FITZGERALD: Okay. Can you hear me?

DR. CASSELL: Very well. Very well indeed.

DR. FITZGERALD: Okay.

EMERGING SCIENCE: PREPAREDNESS OR CATCH-UP

DR. FITZGERALD: So I'd like to just build on the theme that Dr. Caskey has spoken to. In the reports we highlight eight areas of emerging science and technology that will present particular challenges and opportunities for the FDA.

And to recap, they relate to a systems approach, to understanding biology, which is closely wedded to reliance on information systems and analysis.

Wireless health care devices, nanotechnology, advances in imaging and robotics. And new advances in products

including cell and tissue based projects, regenerative medicine, stem cell research, and combination products.

And what I'd like to draw your attention to is that while these rapid developments in these areas impinge on all of health care and indeed on the human condition, they have particular relevance to the discovery and development of new drugs.

And furthermore, and what they will require, is an increasing emphasis on interdisciplinary skill sets, and the agency just like companies and academic institutions will need to be able to tap into a critical mass of individuals capable of both integrating and applying information derived from these emerging technology and therapeutic modality to drug discovery and drug development.

Now I'd like to just highlight a few of that these have immediate relevance to the drug discovery and development process.

Tom has spoken to the rapid drives that have already been made since in sensitive and quantitative detection in biological fluid using mass spectrometry of biomarkers of drug effect that are both based on the hypothesis of how the drug works, but also biomarkers that are unbiased by any concept of how we think the drug works.

Now this is a rapidly emerging area which I think we all believe is going to impinge dramatically on our understanding of how drug works, and particularly how they might be individualized in their utility.

Secondly you are all aware of the increasingly cheap access to individual genomic data. Proteomics is a burgeoning area, and there are beginning to be very rapid development in how we can actually apply proteomics in a quantitative fashion, again, not just configured on a hypothesis of how a drug works, but also in a hypothesis free approach.

The bioinformatics capabilities that will be necessary to harness this information presents a particular challenge. And increasingly we're moving to an understanding of biology and indeed drug action that is configured on the intersection of many biochemical pathways in a so-called systems approach.

Now a positive impact some of these emerging science will have on the drug discovery and development process: first of all, they will help and already do help in the rational identification of promising drug targets. And increasingly we will use a diversified array of model systems, different species, different cell-based model systems, for proof of principle of drug action.

We will be able to harness those technologies that I spoke about to project quantitatively a drug concentration-response relationship from those model systems across the translational divide into humans.

And this will expand considerably the efforts that we currently deploy to stratify drug use at an individual level to maximize effectiveness and to minimize risk; the so-called personalization of medicine.

Now where does the FDA stand with respect to these emerging scientists? Well, we noticed three areas in which a deficit is apparent, and indeed a critical deficit is apparent.

The first of these was actually in human capital. The explosion of these new sciences in their own right, but most importantly in a context where they have to be integrated, have really shined a light on a critical deficit in individuals who have the skill sets capable of harnessing this information.

Now I might say this doesn't necessarily restrict the agency. But the relative absence of those individuals within the agency obviously undermines substantially

the potential of its role in the regulatory mission.

So the first critical deficit is in human capital.

The second critical deficit is actually in the reorganization of science within the agency to accommodate the acquisition of this type of information, harvesting relevant information from these databases, and the integration of this information with the regulatory mission fo the agency.

So the second critical deficit is really in organization and integration with the emerging sciences within the regulatory mission.

And of course the third critical deficit is in resources. Because without the application of resources to infrastructure and to the development of the relevant human capital, there is no possibility of the agency being able to plug into this transformational

impact of science on a mission.

So if we consider the emerging sciences of the FDA, what are the needs? Well, the first need obviously is to build internally a critical mass of individuals who are familiar with, conversant with, these emerging sciences.

But it's unrealistic to think that one could recruit and train a sufficient number of individuals with these complex interdisciplinary skill sets who are retained solely as employees within the agency.

So we believe that an important part of this is the new type of scientist that is focused on the emerging sciences within the agency, but is part of a network that integrates them with the community of similarly skilled individuals extramurally.

We believe this is necessary to harness the capability of intramural scientists to deploy these emerging sciences to drug development and discovery.

So where can one turn for those sorts of interaction? Well, we think one area of high potential that is relatively underexploited is the academic sector. Much but not all of the innovative that has occurred in this area of emerging science actually occurs within the academic sector. And virtually all of the training in these new intricate plenary modalities will occur in the academic sector.

Secondly, the academic sector itself by other initiatives has been pushed increasingly to become re-engaged in the process of drug discovery and development. Historically the academic sector actually played a considerable role in the discovery of drugs. But really over the last several decades that has been ceded almost entirely to industry.

But now new initiatives, particularly those within the NIH, which put an emphasis on so-called translational

science, has pushed the interest of the academic sector increasingly back towards drug discovery and development.

So if you will, the time is right.

However to align the expertise that may lie within that sector with the regulatory science mission of the FDA, it is necessary to have the FDA resourced appropriately to be able to garner prompt, and align those necessary parts of the academic sector with their mission.

Additionally we see a great opportunity at this interface as far as education is concerned. On the one hand it is an opportunity to grow individuals with these interdisciplinary skill sets who might be recruited by or interact with the agency.

But the other side of the coin is, increasingly it is important to attract people from that sector to be exposed to regulatory science within the agency.

And of course there is increasing

interest in that sector for that to occur, because of the emphasis on educational science.

So one of the initiatives that you will see within the report is what is called the incubator for innovation in regulatory and information science, or IIRIS. And this would be a structure that would be under the control of the chief scientific officer and would be resourced sufficiently to recruit that critical mass intramurally of scientists within the FDA, that core of interdisciplinary scientists who could then interact in a network with centers of expertise housed in the extramural sector, and different ventures might have particular types of expertise that the FDA would wish to harness.

For example there might be centers of expertise in systems biology and metabolomics and biomarkers and translational therapeutics in regenerative medicine for example.

And these sites could be not only sites for training and exchange, but also sites for collaborative pursuit of programmatic initiative that would add particular value to the expansion of expertise within FDA itself.

So in a way this could be thought of as the sort of Jet Propulsion Lab of the FDA.

So in summary we believe that these emerging sciences and technology promise to revolution both prevention and treatment, with a particular impact on drug discovery and development.

We believe that the FDA needs to institutionalize its approach to this area, both programmatically and educationally. We believe that the academic sector represents a particular opportunity free of many of the trappings of conflict of interest for the FDA if it resorts to engage B to be maximized and invoke the programmatic and educational

initiative.

And finally we believe that neglect of a strategic approach to these emerging sciences will impinge rapidly on the ability of the FDA to fulfill its regulatory responsibilities to the American public.

DR. CASSELL: Garret, thank you so much. Very well said.

Our next speaker and the next subject is one that I alluded to as perhaps the weakest link but the most critical link in terms of advancing science and returning FDA to its standards so that it can lead us instead of playing catch up.

The next speaker is Dale Nordenberg. Dale is a pediatrician by training, but yet has played a very extremely important role at the Centers for Disease Control in preparedness for not only bioterrorism but also an influenza pandemic as far as putting together the information technology infrastructure.

In other words he's very well aware of the challenges of putting in place IT systems in complex organizations. And he just in fact in the last six weeks joined the private sector, and is looking at it from different eyes now, but will talk to us about what the findings were of the information technology subcommittee, or sub working group.

I might also add that if it were not for Dale you wouldn't have the slides you have before you today, and our report wouldn't look quite as professional as it does. I learned a lot about my inadequacies in IT in working closely with you, Dale. Thanks again for all your support.

INFORMATION INFRASTRUCTURE: THE WEAKEST BUT MOST CRITICAL LINK

DR. NORDENBERG: Thanks, Gail. I hope that wasn't an advertisement to do PowerPoints for the group.

(Laughter)

So I'm not traveling in space to

speak to you today, but I feel like I've traveled in time with Gail over the last several months, and also certainly have followed Gail around the globe; but virtually as this report was being prepared.

And I would echo what Ken has said in terms of the incredible amount of time and energy that Gail has put into this report, and it's been a privilege to work with Gail and the group, and it's also been one of the most rewarding activities I've participated in professionally.

I would also like to say that, as Gail has mentioned, coming from CDC, and coming from government, and managing technology, I'm probably, as we started to meet with the information technology professionals at the FDA, I probably had as good a seat as anybody to have a sense of the state of IT and IT competency of the agency. And I would say that it took but a few minutes to realize and to develop incredible respect

for the information technology folks at the agency.

So while we will be identifying significant gaps in the information technology infrastructure, I think that our colleagues and the scientists that have spoken before me have enumerated many reasons why the information technology challenges are very significant. And again, I'd like to reiterate that I believe that there has been some important progress perhaps too slow, but important progress by very competent people in the information technology arena at the agency.

So if I were standing up here, I could pretend like this, if I were standing up here with a black box, and I said to you, this had a couple of wires sticking out of it, and I said, guess what, I can solve all of the FDA's information technology problems, and we can catapult science and the FDA to the next century just by plugging this in, probably

half the people in the room would say, where can we plug it in and when, and the other half would say, you're crazy.

This is the challenge of managing technology and science today. So both groups are perhaps right. Fifty percent of the time one group will be right, and 50 percent of the time the other group will be right.

Let's see if I can figure out how to work this technology.

So what I'd like to do is start out and level set, because one of the things I find when scientific groups come together, and many people come together, is that the definition of technology varies, depending on which chair you're sitting in.

So one of the interesting things about information technology, it has three different roles. It's an infrastructure for the FDA. I mean you need engineers to put in essentially the plumbing to move things around.

But it's also a science. You need the informaticians to help push forward the molecular biology and the other emerging sciences.

So there is clearly a scientific component to the IT agenda.

And then in addition the third hat that IT wears, it's a regulated product. When you have a device that you are putting in someone's chest that is moderating heart beats and beaming that across distance to another device that's receiving it, now technology actually becomes a regulated product.

I think that's important to bear in mind as we move forward through our discussions.

So in terms of the IT arena, what I mentioned here is that we think of IT in the context of supporting programs, and then we think of it in terms of supporting infrastructure, infrastructure being boxes and wires and the management, and obviously the

programs being the day-to-day regulatory mandate related activities of the agency.

In terms of scope, again, just to level set, the scope here really is referring to components. These are the various components that one must touch when one is dealing with an infrastructure related to information.

These are the databases, these are the hardware, the software, and so on and so forth.

So it's easy. I think perhaps because we all have computers on our desk, and most of us I don't know if anyone does, but most of us don't have mass specs on our desk, you know.

So it's easier for us to imagine that, you know laboratory science is a whole lot more complicated than doing anything in technology, because obviously we all have computers and databases right on our desktop.

But in fact information technology

which wears these three hats requires the same careful rigor that the science that we practice does. And in fact there is a tendency to forget that.

So this simply enumerates the components. And then the next slide says, okay, if we have these three hats, and we have these two arenas, infrastructure and programs, and then we have all these components, then at the end of the day hopefully you are driven by mission.

And so there are processes that you execute in order to support the mission, whether this be electronic application processing, networks to deal with safety and efficacy; whether you're doing risk detection technology; those types of processes to support the FDA mission.

What is causing these gaps? There are a lot of challenges that have already been identified for science. And since technology wears three hats, anything that is affecting

science at the FDA is affecting the IT agenda.

One, because it's a science; and two, because it has to support the science; and three, because it's a regulatory product, regulated product in many cases.

So vast amounts of data, the emerging sciences, when you think about the fact that every 12 to 18 months the capability of technology doubles, storage capability, processing speed. In two years, now you're four times, right? In three years you are now eight times.

By the time you are 3-1/2 years out you now have integrated a magnitude in terms of changes in your technology capability.

So there is a real challenge historically in how do you manage this rapid pace of innovation and technology. Now what we have is actually the perfect storm. Now as has been pointed out in the genomics arena and in the other emerging sciences, these sciences are moving as fast as technology.

So now you have things changing at multiple entities, multiple sciences, multiple disciplines, changing magnitudes over really a handful of years.

So the challenge here in terms of managing emerging science is information sciences, and then rapidly emerging technology is tremendous when you step back and take a look at it.

Now you get on top of that globalization, which is another gift that technology has given us, because now we're flying all over the place very rapidly; we're shipping things all over the place very rapidly; and how we have even greater stress on the system. We have what has already been mentioned is the challenges of shared jurisdiction, so the CDC, the FDA, the USDA, multiple agencies, are developing systems and perhaps not optimally working together to define areas of intersection.

Now there are a large number of

sites that have to be monitored. As Gail has mentioned there are 300,000 sites that have been enumerated overseas that have some type of role; they produce some product that needs to be regulated. And that is mind boggling, and to think that that could be monitored or regulated without technology I think we can appreciate is almost impossible.

Positive trends but critical gaps: so this basically refers back to what I was just talking about when I launched into the talk, that everybody is familiar with the stories about technology investment that has gone awry. So what our subgroup did is, we took a step back and said, hm, if we have significant gaps, does it make sense, are we comfortable saying let's push resources into to close those gaps?

And so one of the things we have to ask ourselves is what has been the track record. And what we see here is that strong management has been brought in very recently,

which is a very good sign. We see really strong interactions between the scientists and the technology folks at the agency; very good sign. This has resulted in the birthing of effective though embryonic or young governance boards that will adjudicate mission and technology.

The IT activities are starting to decentralize, but they are not there yet, so they are not highly coordinated yet. Standards are in process. There's good external collaboration between the FDA and external standards bodies. Again, it's that whole activity globally is early on; the impact is still too soon to detect.

The recognition of key challenges is fairly universal and consistent throughout the agency, which suggests that people will be able to come together and agree on what needs to get done.

Business processes are getting effectively mapped out, but again it's

embryonic.

Strong collaborations with external partners are forming, especially in the area of standards as I mentioned. And the office of CIO, and the CIO is quite new, just probably with the past year, has already identified five critical initiatives which address many of the issues that we are talking about today.

So we feel that there is good progress but slow progress on the horizon. And that'll be an important point that I'll wrap up with in a couple of minutes.

So I'm going to go through fairly quickly several issues that we have touched on as we move forward, and some perhaps new.

Information supply chains: this is an expression that I like to use, because it actually implies something is getting produced. It's not about putting boxes and wires out there, but somehow we have to figure out what information do we need to produce to

drive quality, safety and efficacy from a regulatory perspective.

What kind of information products do we need to produce to support innovation across the industries that are regulated by the FDA, so that products are coming out so the cures come to market faster, the interventions come to market faster, but they come to market safely as well.

So it's often that you hear people talk about clinical trial networks, distinct from pharmacovigilant activities. But when you really take a step back and you look at the type of data that's collected, it's very similar. And in fact we have to start to look at shared infrastructures that are going to emerge, and it's important to realize that the FDA has two different types of technologies that it manages: internal, you know, they own the building, they own the boxes, they own the wires, they can build a network. That's good.

On the other hand when you want to

build shared health information exchanges across the country or the globe, they don't own all those hospitals. They don't own the pharmacies, they don't own all the clinics. So that becomes a much greater challenge.

But it is an opportunity for the FDA to provide critical leadership.

New science and emerging risk, we've talked about this a lot. I think that the notion of IIRIS, which is again the incubator for innovation and regulatory regulatory and information sciences, is a very interesting concept. One of the issues that the group clearly discussed was the research agenda for the agency. It's one thing for example to say these are the things that the FDA needs to research; it's another thing to say here is a structural entity. This is a structural organization that is being proposed; a set of processes that are being proposed; so that the FDA can in perpetuity identify its research agenda and adjust to the

rapidly emerging sciences and technologies that it's exposed to.

So it's important, if one were to determine or identify very specific research agendas, it's very possible that in several months or a year, they would change.

So IIRIS is interesting in that it gives the agency an ability to adapt.

The other aspect of IIRIS that's important is that it's not just important for science from a chemistry or biology or product perspective, but from an IT perspective. If you don't push IT people into IIRIS, there is going to be disjunction between the IT capability and the science. We are not going to get the kind of marriage that we've talked about.

Food safety has already been discussed. Crossing intergovernmental agencies is critical. The vast number of food lines that are hitting our borders from international sites is incredible. Clearly

food safety requires the technology, if you will, intervention to augment the people or person intervention.

And there are technologies like remote sensing kind of technologies that could be put in place at the site of manufacturing or in transportation vehicles that clearly needs to be developed, and the FDA has an opportunity to take a leadership role in developing those technologies and closing those gaps.

The IT infrastructure of the agency, there is clearly an opportunity to tune up this infrastructure. There have been surveys of the infrastructure prior to our assessment that have identified that as many as 80 percent of the servers have already exceeded their recommended server lives. The servers are often scattered across the agency.

As I've mentioned, while this is a serious gap and has caused, or could cause significant problems, one of the things we see

is that already there are activities that have been put in place that will start to rectify it. The question is, how fast might that occur without sufficient resources to support the excellent capabilities of the folks on the ground.

The other aspects of that would be recognition that technology has evolved as fast as the genomics arena or faster. We know that barely 10 to 15 years ago nobody was using emails, mid-`90s nobody was really using email. There as hardly a worldwide web.

Today we are about to experience an overloading of the Internet because of the amount of video content that's moving around. And certainly we can appreciate why for example the FDA might find itself, like many agencies and corporations, trying to figure out how to evolve its infrastructure sufficiently quickly as we move forward.

From a workforce improvement perspective, I don't need to spend a lot of

time on this. It's not different from the issues that were already expressed in the science discussions.

Tight integration with IIRIS and informatics training program, same type of concept, would be two of the most important things we might talk about.

One of the things that we spoke with folks during our interviews about is the opportunity for FDA as a regulatory agency to be able to work through legislative channels to help progress and propel standards that would promote health information exchanges; to promote or support remote sensing kind of technologies, or to support types of things such as e-pedigrees.

And there has been some legislation for some of these, including the e-pedigrees. However the complexity of trying to get industries, governments, domestic as well as international, to start to adopt these types of technologies is certainly not trivial;

again, a big opportunity.

So I'm going to come back in this last slide to this concept of a rationale for recommending investment. Certainly there are critical gaps, but we have already as I mentioned identified evidence of significant commitment, significant capability, and some early progress.

And we have already talked about the fact that there is new and strong management that has been brought onboard in the information arena.

And so I think that it's accurate to say that the subcommittee believes that an investment in the IT arena would be capable of being managed by the folks at the FDA, and that it would ultimate be able to have a very significant impact on regulatory science and the regulatory mandate that the FDA is challenged with daily.

Thank you.

DR. CASSELL: Dale, I hope in the

discussion you can come back to maybe commenting on the warehouses of clinical data that I referred to earlier, and what we think the implications of that are. I know you didn't have time, but that would be great.

I'd like to move now to discussion of the expanding responsibilities but declining resources that have occurred over the last 20 years.

The person that perhaps has the greatest insight into this situation is Peter Barton Hutt, former chief counsel for FDA, someone who was recently declared in the publication called The Hill that he is the utmost authority on food and drug law, and certainly has a love for this agency and a respect for the agency I think bar none.

And we'll just tell you that many a night, many a weekend, that Peter was in his office, way into the wee hours of the morning, pulling together data, and at the same time teaching a course at Harvard on food and drug

law. So total commitment again by one of the committee members.

Peter.

INCREASING RESPONSIBILITIES AND RESOURCE CHALLENGES

MR. HUTT: It has perhaps not escaped your attention that our group is comprised of 32 distinguished scientists and one regulatory lawyer.

At the first meeting of the group I recommended that the 32 scientists focus obviously on what they knew, and obviously what I did not know, namely, the scientific needs of the agency, and that I should spend my time focusing on two relatively narrow but I think critical issues.

The first is the increased statutory responsibilities, as Gail said, just limited to the last 20 years, that drive the science needs at FDA. It is these statutory obligations that impose on FDA the obligation to use good science in the interests of public

health.

And then second, look at the other side of the coin: what resources has Congress given FDA to deal with those science needs? Because if we did not look at those two issues, any report that we might issue would be totally misleading; indeed, I would say fraudulent.

The result is a report that I prepared at Gail's request for the subcommittee. It's 35 pages long with an additional six tables of data that document both the increased responsibilities and the stagnant resources.

Let me begin with just a very brief overview of the increased responsibilities. They come from three sources: the first, and the one that you would be most familiar with would be the statutes enacted by Congress that directly amend the federal Food Drug & Cosmetic Act, or impose related obligations directly on the agency.

Just in the past 20 years I prepared a table, a 10-page table of more than 125 statutes. That's more than six every year for the last 20 years that create new requirements for FDA.

I will mention just one in particular to give you an illustration. It was signed by the president in September of this year. It's called the FDA Amendments Act of 2007. It has 11 separate chapters. It is 155 pages long. And it imposes more than 200 new requirements on the Food & Drug Administration.

This is it is the longest and most complex statute in FDA history.

These are the kinds of statutes that weigh upon FDA and that impose the scientific needs on the agency.

But there is also a series of statutes, and I have a Table 2 to my report that documents representative because I couldn't list them all but representative

statutes of general applicability that also have major obligations on FDA.

And I will give you one example that I know you'll be familiar with. It's actually one of the most important statutes in American history, the Freedom of Information Act.

And you might say to yourself, well, that's a very good statute. It is a terrific statute. But FDA every year spends $11 million implementing the Freedom of Information Act. It imposes not just on clerical personnel but on FDA's scientists an obligation to go through the agency's scientific records and determine what can be made available to the public.

And thus it also is a drain on FDA resources.

And finally there is an area that very few people understand, presidential executive orders. I'll give you just one example. The president this year issued an

executive order authorizing the Office of Management and Budget to review all agency guidance documents.

Now FDA, I don't know, Janet, if anybody has ever counted the number of FDA guidance documents. I've seen an estimate of 3,000.

But in the future OMB is authorized for each of these kinds of documents to issue oversight requirements. This will mean that FDA scientists preparing these documents must now be prepared to defend them at a higher level in government, which means they will be spending more time, and in fact, probably fewer of these documents will be available because of the oversight requirements.

The cumulative impact of all of this, all of these legal requirements, is immense. It is this that imposes the scientific needs on FDA. And these statutory requirements carry no corresponding appropriations. Appropriations come from one

committee of Congress; statutory requirements come from different committees.

We thus often see a complete disconnect between new statutory obligations and no new appropriations.

I list in my report five pages of FDA safety programs beginning in 1960 that remain unfinished because of the lack of scientific resources to make the safety determinations that those programs require.

Now let's look at the other side. Let's look at the corresponding resources that can be placed against these 125-plus statutory obligations that have occurred just in the last 20 years.

We, I will confess, had a great deal of difficulty in quantifying the resources available. FDA has never had a validated budgetary historical database that would chronicle the increase in funds, or decrease, or the increase or decrease in personnel over time.

The database that is contained now in Tables 4 and 5 of my report was constructed as we went along, and I would like to pay tribute to the FDA personnel who labored mightily to help me put together what occurs there.

To my knowledge it's the only database that exists on this subject, and I hope that in the future it will be kept up to date.

But faced with this enormous increase in scientific responsibilities, let's see what has happened. The number of personnel, appropriated personnel not user fee personnel, but appropriated personnel increased over 20 years roughly by 700 people.

And that those 700 people were expected to be sufficient to implement those 125-plus statutes.

The number of dollars did not keep up with inflation. FDA lost money to inflation over that 20 years.

And that is why in desperation the agency beginning in 1992 had to resort to user fees, and why in desperation the industry had to agree to go along with user fees.

But the result of user fees and this is documented in the report has been that some parts of FDA are barely adequately funded through user fees, and other parts, as Cathy Wotecki pointed out, particularly the what you might call the orphan centers, food and veterinary medicine, they are the poor people of the agency; they have been devastated, and in fact, as my report points out, CFSAN has been disintegrating before our very eyes.

Now in conclusion let me say that FDA is the oldest and most important regulatory agency in our country. Virtually every thing it does is based on science. Indeed it is science that leads FDA, not the statutory requirements themselves.

But because of a lack of money and

personnel the agency is now barely I would say crippled and limping along. It is powerless to do the job that the American public expects. It is what I have called in my report the paradigmatic example of hollow government.

Increased expanded responsibilities; stagnant or reduced resources; and thus the inability to undertake the kind of work envisioned by the American people and by our Congress to protect this country's public health.

DR. CASSELL: Thank you very much, Peter. I hope people will read your document, and they are the opinions of Peter, so well informed, not necessarily the opinions of all the committee members, as you might expect, but a very important document for the history records in terms of the picture of the agency that we have today, and a lot of hard work.

Carlos, could you please turn the projector back on? I'd like to just summarize

by making a few comments.

If we could just get back to the last two slides. Yes.

SUMMARY AND RECOMMENDATIONS

DR. CASSELL: So in conclusion it is true that our committee overstepped our charge. We were forced to look at resources. But I hope you can all appreciate why we felt it was so important to overstep our bounds.

We are at a very critical point in our history, and in the history of the agency. Without a significant and sustained increase in funding, the FDA cannot perform its mission. And that is our conclusion.

I will tell you it is absolutely the unanimous conclusion and strong and adamant feeling of every member of our committee, bar none.

Lastly, the current situation has developed over many years as you've heard from all speakers. This is certainly not attributable just to the last few years, or to

this particular commissioner, or the individuals that are here today in the agency, but rather over many years.

The question is not how or why we got here, but rather, how do we strengthen FDA going forward.

FDA staff is highly dedicated to protect the public's health. And again this is a unanimous feeling of the committee, but can no longer fulfill their mission without appropriate tools and personnel.

Just to emphasize the urgency of the situation, a recent report documented that as far as scientific personnel go, FDA has a much higher attrition rate than any other federal agency; and indeed, the two largest centers of FDA are currently without a director.

And I will just say that within the past five years, I think it is, Dale, that there have been four different CIOs.

So I think that what we all have to

realize is that we have some critical positions that need to be filled, as you've heard some every person that's spoken today, that we've heard from all fo the centers as we went through the interview process.

And unless there is some hope that the resources will be available to allow these new leaders to fulfill their responsibilities to the public and to protect the public's health, I fear we will not be able to attract the best leaders that we need in these positions as we face these challenging times.

Again, I would remind you, this committee was a balanced committee representing academia, government and industry. This is not the feeling of a single sector. No single sector stands to benefit anymore than anyone else.

But we as citizens all stand to benefit as we've alluded to in terms of saving lives, and also protecting our security as well as our economic leadership and

preeminence in science if in fact we act now.

The other thing is that this situation I would end by just saying we do feel is urgent, and do agree that the public's health is at risk if action is not taken.

This last statement is extremely important given other reviews that have taken place that have warned unless action is taken the public health's is at risk.

I think you have heard this afternoon from Cathy Woteki one of the reasons that we felt that we needed to say it's urgent and that people are at risk is that those warnings have come to pass. We are living them now, seeing them everyday, and if we don't take appropriate actions they will only increase and not decrease.

Lastly, Ken, I'd like to recommend that the science board accept the report of the subcommittee, and then take further steps to provide the review of in depth analysis of some of the high priority areas that we have

identified.

I appreciate you giving us so much time to share the fruits of our labor this afternoon.

DR. SHINE: Gail, before you sit down, with the caveat that as with other reports I think we ought to provide comments from the center leaders and other management with regard to the report, as a member of the committee would you move the recommendation, and we'll see if there is a second for it before we open the discussion?

DR. CASSELL: Could you just restate what you are suggesting in terms of with the caveat for input.

DR. SHINE: The motion would be that the Science Board, Science Advisory Board accept the report of the subcommittee with thanks and appreciation; that it takes steps to provide further review and have an in depth analysis of high priority center programs, the role of the NCTR, and the scientific capacity

and that it seek additional comment from response to the report from center directors and other parts of FDA management.

DR. CASSELL: I so move.

DR. SHINE: Is there a second to that?

(The motion is seconded)

DR. SHINE: The motion is made and seconded. The report is now open for discussion.

SCIENCE BOARD Q&A AND DISCUSSION

DR. SHINE: I do have to tell you I was delighted to hear about the Cassell-Marks event that you had, since I had the privilege of serving as a member of your committee on that report.

DR. CASSELL: Well, Ken, I would point out to your big surprise that maybe you don't even remember either, that report was released to Harold Varmus, the director of NIH, in May of 1994, and by November we had an implementation plan as did Congress along with

a progress report where progress had already been made in that short a time span.

DR. SHINE: Well, I think it is appropriate to point out that in his remarks this morning, the Commissioner said he was going to look very closely at this report in terms of trying to move the agenda forward.

The report is open to the members of the committee for comments, questions, suggestions.

Susan, food safety, CFSAN.

DR. HARLANDER: Well, I was very impressed with the report. It's very comprehensive. I was pleased to see the report on CFSAN. My responsibility has been primarily focused on food.

I'm in agreement with all of the conclusions around the food side of FDA.

I'm most concerned with your finding and your recommendation, 4.1.2, and it has to do with that the recommendations have not been followed in the past. And I believe

in having worked with this board for four years that that is not because there isn't an understanding of the needs of everything that has been identified by all the folks that I've had an opportunity to get to know over the last four years.

And so it seems to me the challenge for the Science Board goes beyond our recommendations to FDA, and it has to go to how do we influence the political process that confers upon the agency all of these increased responsibilities, statutory and presidential, and doesn't couple that with sufficient appropriation.

And so I'm wondering if your committee, your subcommittee, discussed ways that we can influence beyond the FDA folks and influence the political process. Because I think just building budgetary recommendations into the next round is not going to be sufficient to institute the kind of changes, broad changes, that have been surfaced in this

report.

And so I just raise that and put that out as an issue that I think we need to address.

DR. CASSELL: We did not take this on specifically, as you might imagine, Sue.

I will just say that I think it is up to all of us, the members of the subcommittee, the members of the board, to better educate the public and also the policymakers in terms of our findings and what we think the implications of those findings are. And then hopefully the public will communicate this and their concern to the policymakers.

I think it is all our responsibility, and all of our responsibility to work hard to see that action is taken promptly.

And I'd turn to Ken to kind of maybe perhaps lead us through a discussion in terms of what he thinks the role of the

Science Board should be.

DR. SHINE: Thank you, Gail.

I would emphasize the point that Gail made about education, getting some of this data out and understood by a variety of people is going to be essential.

As I suggested I'm going off the Science Board come December 31st, thank goodness. And that provides me with an opportunity to speak very forthrightly in the political arena with regard to some of these issues, and I hope that other people who have been active in this process will also provide support.

I do want to emphasize one problem. Obviously the media has already picked up on the report which had to be posted on our website prior to the meeting as it was appropriate.

The media of course looks at the criticism and that becomes the headline. On the one hand that may be useful in terms of

getting the attention of policymakers and other leaders in terms of addressing the problem.

The risk of doing that however is that you don't necessarily indicate the respect and appreciation that the agency deserves as it does its own work.

So finding a balance between making it clear that there are enormous opportunities, and I would emphasize to the board that although the executive summary talked about perhaps generalities, IT and systems biology, et cetera, et cetera, that the appendices have a good deal of detailed information about scientific opportunities. And I think in that regard it was responsive and is responsive to the commissioner's charge.

But I would say, Susan, and unfortunately the way either the media or public policy works is often not in a balanced way, that we not lose sight of the fact that

this is a very good agency which is being, for the reasons that Peter Hutt very articulately explained being stretched and stressed as the Commissioner said this morning, and is in real danger in terms of being able to conclude its mission.

And I think getting that across in the appropriate venue is going to be very powerful, and I hope that not only members of the board but others there were 30 very distinguished individuals who were consultants by virtue of their learning about the agency and so forth I hope they will be adding their information and knowledge to the educational process.

Others may have other ideas or suggestions.

Other comments?

DR. SASICH: Thank you very much.

I'd like to express my gratitude to the subcommittee for the job that they did. I'm a new member on the committee, and a

consumer representative. And this was a Herculean task, and one that was very important.

I think in terms of some of the issues, particularly some of the issues that Mr. Hutt had raised about prescription drug users fee, that is an old issue for a lot of consumer groups. That goes back to 1997 a large number of consumer groups were very much concerned about the reauthorization if PDUFA and its effect that it would have on the agency over time.

It didn't get picked up by the news media. And that's part of the problem. In this last round of reauthorization of PDUFA not much was written about consumer groups' concerns about PDUFA.

But I suppose the thing that one of the things that came to mind to me last night was the policy process and how it might be influenced.

The public, and in the form of

consumer groups, has been pretty unsuccessful in being able to get people on Capitol Hill to listen to the problems that were so precisely outlined in Mr. Hutt's report.

Would it be possible that in future meetings of this group, maybe one meeting a year, that we have people from the Appropriations Committee, people from the committees of jurisdiction over the Food & Drug Administration, and we regularly in service them so that we could at least get a feeling whether they actually understand the issues or not.

I think one of the biggest problems that the agency has always had is, it hasn't had the resources or the opportunity to be able to communicate directly well, I won't say that, not directly but it doesn't appear from the outside looking in that the agency has been able to make the arguments that need to be made in a way that's understandable by the people that appropriate the money.

And I think it's absolutely critical. We need to find a way to get to those people so they understand the issues that were raised in this report. They are absolutely critical.

Thank you.

DR. SHINE: Thank you, Dr. Sasich. Others may want to comment. My response would be, first of all, it is unlikely that staffers or others are going to agree to come regularly to a meeting of this board to be schooled.

On the other hand given the nature of this report, I would suggest to the Scientific Advisory Board and the Commissioner that it may be useful to ask some key folks to join with the board at some future meeting and ask their reactions to this report in terms of both the analysis and the recommendations.

That I think would be fair. I think could be constructive, and in fact, giving given some feedback presumably they would read the report before responding.

That would be just one thought that I would put on the table.

DR. SASICH: I don't disagree with you. I think it's going to take more than one meeting. These are enormously complex issues.

DR. SHINE: I don't disagree at all.

DR. SASICH: I was just searching for some kind of mechanism where at least we have some kind of assurance that Congress does understand these issues.

A lot of the public understands these issues, and spend a lot of time with them. We've never been able to get the seriousness of this issue across to the public.

The thing that we are worried about now as what has historically been part of drug regulation in the United States, we wait for a tragedy and then we react. And the basis the way the system seems that it was designed to evolve was that a science-based regulatory authority would use the science to be able to

predict that there is a big risk out there, and we need to do something.

We need to find a way to be more proactive, and the system has got to stop being only reactive.

DR. SHINE: Thank you, Dr. Sasich.

Other comments? Allen, you were a member of this group. You're on the subcommittee. Do you have any additional comments that you want to make?

DR. ROSES: Yes, I do, but I'm not much of a politician.

(Simultaneous voices)

DR. SHINE: I am not either, but anything about the report or any aspect of it, or the science or whatever.

DR. ROSES: Yes, as this was going on I saw an emphasis that I hadn't realized as part of the committee; is that this is really a lack of parity between our overstepping our mission and trying to explain why and how these things can happen with regard to

budgetary issues.

I have a pacemaker so I get a little worried.

Okay, that fixed it. I fixed it. The parity between that

(Interruption)

DR. ROSES: No, they just sent me a notice that said the wires that I have

(Laughter)

DR. ROSES: By the way.

I think the issues are so monumentally important, that it was so monumentally important to the committee to put this into perspective that sitting by the science alone, and detailing the deficit without strongly putting some of the reasons and the resource issues on the table would have only seemed half of it.

And I am wondering why we are apologizing for it. One of the things I remember that struck me as very, very odd when we went, when Peter Hutt went through one of

his histories at one of our meetings over the telephone was that there was considerable worry about whether we would have a report that would be read.

I understand my history of this isn't as deep as it should be but I understand there were reports in the past that went to one of the FDA directors, apparently, and wasn't even accepted.

I would think that that would be a shame. And I feel very very strangely in saying that in the absence of the Commissioner. But I think were he here I would basically say that.

There is a tremendous amount of work about it from a tremendous amount of horizontal and vertical issues that went into the thoughtfulness of this report, and I believe that there ought to be a mechanism of carrying it forth to the legislature and to the politicians that are responsible for making things happen.

I understand that the FDA is not allowed to lobby. But those of us who were now I'm in the academic section I started this, I was in the industry section, I have gone the other way those of us who can do this really ought to find some meaningful way of continuing to put this agenda forward. Because things are really at risk. Imagine if melamine occurred simultaneously with one other thing. Just imagine. We wouldn't necessarily be talking about 300 dogs or cats. We might be thinking about thousands of people. This is untenable; absolutely untenable. And our focus ought to be what we should do about it, not necessarily how we came to it and not necessarily why we phrased it the way we phrased it.

But it's the outcomes that matter, and the predicted outcome from no attention to this matter is devastating.

DR. SHINE: I'm going to ask Barbara as a member of the subcommittee also to make

any comments she'd like to make.

I would one the one hand I think the Commissioner has every right to get additional input from center directors and others with regard to specific recommendations and so forth.

But at least the tone of his comments this morning were that he was he had commissioned this report. I think he's going to look at it very carefully. I don't know, as with any leader, that you can guarantee that someone is going to totally endorse a report.

But I certainly sense from him an openness to look at the logic of these recommendations.

And I think it also is important that you've emphasized that his degrees of freedom with regard to corporate lobbying for additional money may be limited. On the other hand there are four graduates of this Science Advisory Board as of this year, and there also

are opportunities for individuals who are, as private citizens, have every right it seems to me to educate.

And I think education is a very important part of what our responsibilities are.

Barbara, do you want to make any additional comments?

DR. McNEIL: I don't think I can say too much more, Ken, I'm probably being redundant. But the committee was just enormously thorough. And I don't think Gail mentioned that there were several subcommittees that worked in parallel and therefore had the opportunity to dig much more deeply than they would have if we'd been working as a committee of the whole.

So I was on one that had to do with the evaluation component of things. And hearing in my committee, and looking at the results of the others, it was quite clear that everybody did an enormously thorough job, and

at the end of the day I personally and I think most of the other people did came away with just an enormously greater respect for individuals at the FDA than we had before we started.

We always had respect, but it just went up multiples as a result of our appreciating the amount of work that they had to do. So that was just I think tremendous.

Our concerns were two analogous, raised, one was an enormous number of needs that have to be met, and Gail and the various speakers mentioned them.

And the other one though was the concern that they just might not get enough attention, and how we would move to have that happen is what I think we were all concerned about.

So thoroughness, gratitude and concern.

DR. SHINE: Other comments from any other yes, Dr. Linehan.

DR. LINEHAN: So this just my first meeting. So I read the report with great interest. It was really a wonderful report. It was very deep, and there is a lot to digest in the report.

One of the items mentioned which was a little concerning to me was the Harris poll showing that the public's confidence in our regulatory process has decreased.

And it was somewhat of a surprise to me. Because in my perspective, in the work that I do, I've always had an increasing respect for the regulatory process as it has gone on.

So I think this is a serious problem, and someone brought that up a moment ago, that what tends to get in the paper is not the good news but it's the bad news. And if I had the answer to that I probably would be a billionaire trying to figure out the way to do the right public relations pitch.

But I think we're going in the

right direction in this report with the fellowship program, and that is something that looks to me that it's implementable. It can have an enormous impact by bringing in a thousand fresh faces, young men and women from the universities and other settings, to infuse some new ideas, some new peoples into the mix.

That might have some public relations value in and of itself. But the young people of our country I think are very interested in public health. In one of my former lifetimes at the Whitaker Foundation I had a chance to visit most of the major research universities. And the young women and men in engineering are very much attracted to bioengineering, because they see it as helping people.

So I think the attitudes of the young and people are very much supportive of the responsibilities to mankind so to speak to develop new products and so forth. And I think the FDA does a great job also.

I would compliment I haven't met everyone, but last year I was commissioned by the Institute for Health Care Technology Studies to do a study of how medical devices are developed. And in addition to interviewing many people from industry, all the way from entrepreneurs, physician-scientists, physician-inventors to presidents of companies, I found very much a uniform respect in general for the FDA.

The idea that the quality system regulations that have been put in place with the design of medical devices have been very much I think appreciated by in general by industry because it does give a way to systematically do a good job in developing medical devices.

And in addition the guidance documents were very much appreciated by those who are working to try to bring innovations to the public.

So the FDA is doing a great job. I

think the people, at least in the CDRH that I had mentioned, are smart people. They really have the public interest in mind.

The problem is that it is understaffed as I see it from reading the report. We don't have the resources to do the things that we need to do to step forward. A couple of people mentioned today about what's going to happen in the near future.

I was also listening to a few people remark about what happened 15 years ago versus what happened now. And from the technology point of view, remember 15 years ago we used to be talking into shoe boxes. They used to be called cell phones in those days. Now you can't even find them they are so small.

So there is going to be a rapidly increasing technology that is going to drive medicine, and so we have a responsibility to the public I think to make sure that this report gets actualized, and the FDA gets the

resources that they need.

Thank you.

DR. KING: Sure, thanks. Yes, I think both for CVM and CFSAN, a couple of comments.

I think after Cathy Woteki described those two centers are orphan centers, I think we get an idea of what I knew was happening but maybe not that intense. I think it's a travesty that unfortunately those terms are apropos, and it's truly unfortunate. The gap between what has to be done by government, and what it's mandated and what it really can do is a growing distance almost on a daily basis.

And it just seems to me that we've talked about I think it's more than a tipping point. I think it's already started to lean over in the wrong direction.

We've talked about the idea of getting to legislators and appropriations committees, and why we always jump to that

conclusion, because they have the money and it is important. It's been kind of an unproductive strategy in the past.

And it seems to me that those impacted, which is the public safety and public health, which is really at risk, are the ones who are going to have to step forward and really think about doing something on behalf of this agency and certainly those two centers.

So when you consider a world where this agency would unfortunately be broken or nonfunctional, our public would really not be very well served. And unfortunately, that's probably a feasible outcome.

So I think there are three things I'd like to see done. One is a national communication strategy. This has got to be put out in front of the public's idea as a national strategy, and I think a conversation. It has to go beyond Congress.

The second thing is the capacity,

and just thinking about CVM, and what's kind of brought us down into this really serious problem is the lack of that critical capacity, and that is the first step that is going to help us climb out. And that came out loud and clearly in the report, hiring the critical talent that's needed.

And third thing is just to make sure that there is an execution strategy that goes with the plans.

DR. SHINE: Many of us on the board are members of other organizations, have various constituencies, and should the board accept this report as the motion calls for, it seems to me we have an obligation to disseminate that report widely in terms of those organizations.

And to the extent that there are opportunities to network that, that seems to me to be entirely appropriate.

And I think a number of people, particularly members of the committee, are

likely to be asked for comments and so forth about this. I think as private citizens they ought to be able to do that in light of the importance of this activity.

But I think your three points are very relevant. I asked Cathy to come back to the table, because when she started this activity she was not a member of the Scientific Advisory Board. She now is. So now Cathy, in addition to talking about nutrition from the point of view of a nutrition expert, you can provide us your wisdom as a member of the Scientific Advisory Board if you want to make any additional comments.

DR. WOTEKI: Well, perhaps just one, and that is to reinforce the comment that Gail made in her introductory comments about the committee dynamic.

In this case the committee did review all aspects of science across this incredibly complex regulatory agency. And

although we worked in subcommittees, when we brought forward our draft reports, and when Peter introduced the analysis that he had done on the legislative requirements, and the resources, when all of that was brought together, was when the committee I think came to the realization that the situation is as immediate in its need for attention as has been communicated today.

So I really do want to say that I believe that this report is one of the best reflections of the dynamic of a diverse committee that when it brings together an enormous amount of data and has the time to actually sit down and reflect on it comes to a set of conclusions that very few of us as individuals walking into this assignment perhaps would have made.

So again I think it's a reflection of the data and the time to consider it, and also, urge that the committee's recommendations be given very serious

consideration.

DR. SHINE: Thank you, Cathy.

David. Dr. Parkinson.

DR. PARKINSON: I must say I thought this was an excellent report. As I read it I came to the understanding that it had both diagnostic and prescriptive elements.

I can tell you, even though as someone who has interacted a lot with the agency over the years, the diagnostic elements were revelatory. The range of responsibilities, and the declining support by the government in terms of resources for this agency.

Yet to Gail's point, this is basically a prescriptive document. It outlines a blueprint by which this agency, in a time when medicine is changing, when elements around the food and veterinary world are changing quite rapidly, so the complexities are changing, this document does represent an historic blueprint as a basis for discussion going forward.

And I think that it would be irresponsible of the committee to send such a document forward without trying to bring to the American public the fact that without additional support, this agency cannot meet the expectations of the public.

So I think the two go together, but I must say I really personally would like to thank the subcommittee members for what I think is an historic document that really represents a blueprint for one of the most important federal agencies to at least consider as it begins to reinvent itself, which many of the institutions in biomedical research are having to do because of the new biology that Tom talked about in any case.

So I think other agencies should be envious of having such a macroscopic look. But all of this will be meaningless without resources and support.

DR. SHINE: Xavier, do you want to make any comments?

DR. PI-SUNYER: Yes, I'll just mention first of all I'd like to salute and congratulate the group who put this together. I also think it's an outstanding document.

I am left with two statements that I think were made this afternoon, one is by Mr. Hutt who talked about hollow government, getting increased responsibility with decreased resources, and therefore, not having the ability to do the job appropriately; and then comment by our consumer representative that we wait for a tragedy and then we react.

I think also I'd like to recall the statement by Gail Cassell that there are enormous opportunities here, and I think it would be a tragedy if we don't take this report as an enormous opportunity to move ahead and help the agency do the job it needs to do with the resources it requires.

DR. SHINE: It is interesting, there was at least one recent history of the agency on the occasion of its 100th anniversary, and

the comment is absolutely correct that every major legislative change that has taken place in the mission of the organization has occurred after some series of tragedies of one kind or another. And it's unfortunate.

More recently I think the safety issue is one of the driving forces. The difficulty we have is how we in fact anticipate the needs before we have those kinds of crises.

But again Americans like to fund disease management; not prevention. And that's one of our challenges.

Before I call for a vote, I want to ask Gail if she has any benediction?

DR. CASSELL: No, other than to thank you, members of the Science Board, for reading the report. It's long, too long, we would argue, but also for your thoughtful comments.

And I am appreciative, and I certainly will relay those to those

subcommittee members who were not able to join us, and again, thank the committee, subcommittee, as well as the FDA staff.

You should know that Janet Woodcock came into work was it two days, Janet, or one day after your knee surgery. And I can appreciate that, and it was in part because we were putting more work on the agency in terms of information we needed in short order in order to have accurate information to make to draw our conclusions. So thank you, and I look forward to hearing the response of the Science Board.

DR. SASICH: Can I just make one brief statement?

I kind of sense an educational moment here, since we have the media in the room. The Congress of the United States has the constitutional responsibility for making all of this run. They have the responsibility to appropriate the resources, and they also have the responsibility for oversight.

On November 2nd, or on November 3rd, I think it was, we've had the 20th new drug approved since PDUFA was passed in 1992 withdrawn from the market for safety reasons.

People can quibble about the way I counted number 20. There are at least another four drugs that remain on the market in the United States, approved since 1992, that were removed from the markets in foreign countries but remain on the market here.

I think the press needs to understand that it is very easy for members of Congress to use beating up the FDA as cover for their lack of interaction in terms of appropriating resources for the agency.

Saying that, I'd like to make only suggest one amendment to what's on the floor; and that is that we do consider some statement that we will try and move this report forward into the public sector so people do understand what the stakes are that they are facing; if we could add that as part of the motion that

is on the floor, I'd appreciate it.

The motion that is before the committee. Is what's before the committee trying to carry this message forward to the public and to policymakers.

DR. SHINE: Well I'm sorry? I think we have a motion on the floor.

(Remark off mike)

Let's do that. I'm going to call the question on the motion that's on the floor, and seconded.

All in factor, aye.

(Chorus of ayes)

DR. SHINE: Opposed, no? Abstentions?

The motion is unanimously approved.

The Gail, some of you may know that Gail broke her leg skiing in the middle of all of this. And she was in bed trying to put this whole thing together while and then subsequently did it while limping around on crutches. That's real service.

I want to really express my appreciation to her, to the other members of the committee, but especially to her for the load that she carried; to the consultants that worked so hard.

I do think from my recollection of the telephone conversations I was on, although there may not have been unanimous support for Peter's appendix, the support was pretty widespread on the committee. I thought the overwhelming majority of the members of the committee did support his analysis.

And even though it's an appendix, and there was some debate as to whether it should be included in the substance of the report, it was decided to make it an appendix, and I think that's appropriate since it was individually authored.

But I believe it was the consensus of the group to support it.

DR. CASSELL: Ken, if I could just interrupt to say, I probably didn't say it

very well, but absolute consensus in terms of his conclusions. There were a couple of points, but not related to the conclusions or the analysis of the data. So thank you for bringing this up.

DR. SHINE: Carlos, Norris, Janet, we owe you. I mean you really did do a terrific job in supporting this activity, and I think we are very grateful to you.

I would like to make a couple of suggestions for follow up. Keep in mind I'm a lame duck so the committee can do whatever it wants.

One, I would like to see the report reduced with help of the agency to four pages. I'm quite serious.

(Laughter)

It doesn't have to be small print. It doesn't have to be on a chip. It should be in an easily readable set of bullets, because when you are trying to convey this kind of report, whether it's to public

policymakers, or a community organization or whatever, you've got to be able to say it in a form and this goes to Larry's concerns you've got to convey it in a form that they can pick up and look at the front and middle and the back and close it up.

And I can tell you I've had plenty of experience with reports. I think it will be hard to distill perhaps, but in fact all you want is a series of bullets about findings, and bullets about recommendations, and who did the work, and use that document for purposes of education and so forth.

Even the executive summary, as succinct as it is, it is too long for many people to read. And I just I really do believe that putting in a little effort to producing a very brief version of this with some major meshes will help a lot in terms of Larry's concern about education. Because if you do that you know, I recently did a report in Texas on access to health care in the

uninsured. I printed 750 summaries. There were requests for 4,000. I then produced four pages, it was distributed almost 10,000 four pages on request. That's what people want to hand out at meetings and things of this sort.

So I would just urge you to look at doing that.

Secondly, I would also like Carlos and Norris with Janet's follow up of this to solicit responses from Center directors as we discussed in the motion. But also, I would ask you to work with the committee with regard to follow up specifically as it relates to ORA and NCTR so that we don't lose that in the transition that we are sure that we do the follow up in terms of the in depth which your motion suggested.

And finally I would just emphasize that after the process is completed, and we've had input and so forth and so on, the key I believe, and you've already got all the ingredients to it, the key in dealing with the

Congress is not, we need more money; it's we have to have funding to do the following things which are at risk.

And I think a high degree of specificity in terms of how and in what way you connect your report to the funding is going to be essential for those who in fact are going to communicate our message.

But my own experience has been sitting in front a congressional committee and saying, increase everything X percent or whatever is likely to get you relatively small amount of attention.

On the other hand saying that you need significant resources and that this is the agenda that has to be played out, and invariably staffers or others are going to ask you, for what, for what part of this.

And so I think we need to think some of that out as this goes forward. Keep in mind that we still have to get responses from within the FDA and so forth. But I think

that combining the vision as you've articulated with the requirements for resources is critically important in terms of making the case.

DR. CASSELL: So Ken, while you are have been talking about a shorter version of the executive summary and being more specific in terms of linking needs with actual resources, you were looking at me the whole time.

DR. SHINE: No, no.

DR. CASSELL: No, but I'm wondering, and I just want to ask specifically just for guidance, were you looking to the subcommittee to deliver these two requests? Or were you looking to the agency to deliver those?

DR. SHINE: As I understand the motion, we accepted the report, and as a subcommittee, at least that I appointed, I'm prepared to dissolve you, okay? I think you have done your work very well.

I would request that perhaps as an

individual you work with the staff on a four-pager, because you know this report very well. And this is about, this is communication strategy. And you know, if you tell me frankly I've never seen a report no matter how complex you couldn't reduce to four pages if you really wanted to. But I think if you take six pages, that's your business.

All I'm saying is, I think if you want, and I'm picking up again on Larry's observations, if you want a communication strategy you must have some kind of material, and I would say once you agree on that you put that up on the website, because there are people who will not download a whole report, but may download your four pager or whatever in terms of the communications issues.

I mean this is is there any? Yes, please, Susan. Susan and then Norris.

DR. HARLANDER: I guess as part of that, I think it's a separate document, but I think you talked about a summary of the

recommendations of this report.

But having been involved in trying to communicate directly to the public about genetically modified foods for about 30 years with not a lot of success, if we really want to communicate directly to the public, there were a few very very key facts that I think would capture why what you are proposing is so critically important.

And it probably doesn't have to do with any of the recommendations that you actually come up with. But it and it could be captured in about six bullet points out of your report that would be a compelling communication directly to the public that probably doesn't contain hardly any of the recommendations that this committee actually came up with.

And I think that's an important one to really focus on too, because you know, one and a half cents for everything that this agency does for us in terms of food safety and

drugs and health and health promotion, you know, is a very small amount. And the public can get their arms around and their minds around listening to Cathy having to go through all of this education to understand how important the FDA was. And I heard the same thing from several other people, that expecting the public to embrace everything that is coming out of this report is not possible, unless you can capture it in a few bullet points that really become compelling enough that they are willing to contact their congressman and say, what's going on here? And why don't they have that support?

So I think we need a summary, but I think we also need some public relations people that can help capture the essence of the importance of this agency, and something that all of us could use to pass on to all of our e-mail contacts about the importance of this that will compel people to actually do something personally about it. Because I

think that's how it's really going to happen.

DR. SHINE: Susan, the committee, we are not going to write this paper. But I would argue that everything you need is in this report. And I think if you have if you do decide to do a full page version you can pick out of that what the agency is, what it does, why it's important, what the the fact that there was a group that looked at it, what the findings were, and what the recommendations were.

And it simply it's simply a synopsis of the report. I think we will do a lot of the things that you are talking about.

But again I don't believe that we should be writing documents. But I would suggest that that would be a useful way to summarize the report that goes beyond the executive summary; let's put it that way.

Norris, you were going to make a point.

DR. ALDERSON: Since this is a

public document now, I think we can fully expect to receive some comments from the public. And I would ask you and the board how you would like us to dispense with those comments.

DR. SHINE: Gail, what do you say?

DR. CASSELL: You dissolved us.

(Laughter)

DR. SHINE: I didn't ask the subcommittee to do it. I'm asking for your advice.

DR. CASSELL: I believe it's extremely important to hear not just from the public but also the many stakeholders. It was our original intent, as you may recall from very early conversations to have that input before writing the report. But I must admit we are somewhat biased in wanting to analyze the data being asked to look at the science to make our best judgments based on the data, and then to have this input and comment from stakeholders that sometimes are not based on

data but rather strong desires or wishes.

So it is time to have that input, and also, not just from the public, but stakeholders, those that you want to hear from.

The best mechanism by which to get that, I think, might be in the form of another meeting like this, but to welcome input from those individuals in terms of making public comment. I mean this is not uncommon. We do it in the Institute of Medicine, National Academies of Sciences. You know once you have a report and it's issued, then to actually get feedback on that, and take it into consideration as you determine and establish further priorities.

DR. SHINE: Norris, what I would suggest is that when you get the material, if you would and your colleagues would sort that material into there will be classes of questions, whole groups of questions about particular activities.

And if Gail is comfortable with it, I'm perfectly happy on the written side to go over with them the classes of questions. And then between you and I we can decide among the consultants and so forth who might be most helpful in answering those questions. And we'll try to have a mechanism to respond.

DR. ALDERSON: Granted that we will likely get questions, as just a matter of the report being public, what is your thoughts about seeking public comment?

DR. SHINE: Well, I think that goes to the point that Gail made. I would endorse her notion that I think it would be very useful to specifically seek public comment. And that's another way that you reach the public is by asking the public to talk. I agree.

DR. CASSELL: I will say, Norris, that I have had e-mails from people that have seen the articles in the news, and then go to the FDA website and say they spent as long as

an hour but still can't find the report.

So even with the link, and I must admit that these are from some pretty knowledgeable individuals, and I think that one would need to certainly make it a lot more readily accessible if you really want to get them to read it and comment on it.

DR. SHINE: But I do, I would think the idea of having mechanisms for public comment would be very valuable whether at the next meeting or at some other kind of venue. I think both of us agree with that.

MR. HUTT: Norris, as you know there is a well established mechanisms. You could open a public docket site and receive public comment, and put just a short notice in the Federal Register inviting public comment. That has been done in many instances.

DR. SHINE: Yes, the dilemma that has, Peter, is that that then raises the question we were talking about before of responding appropriately.

MR. HUTT: No, quite frequently this is just to gather information. There is no need to respond.

DR. SHINE: Very good. Janet?

DR. WOODCOCK: My question about this is, simply, at what point do we want to do that? Okay, right now the report is before the committee, okay, and there are going to be additions to it. When it is in a final state I'm sorry, when it's more in a final state, then that might be the best time then to seek public comment? Or you could do it now as a part of your further deliberations.

And I think we are open to either approach; we would just need to know what the committee would like. We can do this at any point.

DR. CASSELL: I guess I didn't understand that. I mean I thought the report was accepted by the Science Board

DR. SHINE: It is.

DR. CASSELL: as a report.

DR. SHINE: That's correct.

DR. CASSELL: But I didn't understand then it will be modified by the Science Board without a possibility of the subcommittee being able to respond to that modification.

DR. WOODCOCK: Okay, I mean the ORAP. There are some additions that are going to be looked into, correct?

DR. SHINE: That's what we're talking about. And again, I would think that if the timing works, the next meeting of the Science Board might be a good time to have public comment which would be relevant to it at that stage.

Any other comments? Barbara.

DR. McNEIL: I guess I would argue for sooner rather than later. So I'm not sure when the next meeting is. But it's got to be March or April? March? It would strike me that if we are worried about extra appropriations, then I would want to I would

think we'd want to get public opinion with the document that we have now if there are additional things that are going to be added, fine. That can occur later.

But I would just go out as the holidays, just try and get as much as we can, so that we can then go for it.

DR. CASSELL: I actually endorse what Barbara's just said. We need to do it today, as soon as we can get it in the Federal Register for public comment, as Peter has suggested, that would also be my recommendation, only because we know from the major events that have happened from the time we started the report until now, things happen so rapidly that completely change. You don't want this report to become stagnant before people have an opportunity to comment on it.

Months seem like years.

DR. SHINE: Clearly you could have a website for comment at the kind of Peter talked about very rapidly; there would be no

reason to delay that.

I think the issue of a public meeting becomes a logistical issue in terms of when or how you under what auspices you do that, in terms of who is going to be there.

I guess you could have a meeting of the Science Board early in January or something of that sort for purposes of doing this.

DR. ALDERSON: I think there are two says to do this. One, we could put up a Federal Register notice as Peter talked about, ask for public comment by a certain time, and you incorporate, somebody incorporates that into the report, or you add that as an addendum.

A second option including the first one is at the next Science Board meeting, that becomes a public meeting for anyone to come speak at that time also.

DR. SHINE: Yes, but all we're hearing is the interest is there any

potential for a public meeting any time earlier? Next Science Board meeting may not be until April or May. And I think the question is, is there a potential to do something earlier? I don't know the answer to that.

DR. CASSELL: I would just look back at what happened with the critical path. And I'm not wanting to play that. Although I watched it from early days until now. It seems to me you posted that very quickly to the Federal Register after its announcement in March of 2004. And if I'm not mistaken, you got a lot of input. And I don't view this really much differently than the critical path. It's a blueprint much like the critical path was, and I'm hopeful that maybe the response to this report will be as you know voluminous as it was to the critical path, with very good insight from the public.

DR. SHINE: And if you did that relatively soon you'd get some notion as to

whether and in what circumstances you would have a face-to-face public meeting. All right, that makes sense.

Okay, Lonnie.

DR. KING: Another thing to consider, Norris, would be something maybe more creative that's not Washington based. And that may be you know we are talking about incubators and innovation. There are some really good methodologies now about citizen engagement. There was that one the other day in New Orleans that had five cities, 10,000 people, in one day actually came out of that meeting with input, recommendations and consensus.

Very powerful meeting; every city that was engaged had its own communication strategy and people involved in newspapers and media.

It's one way to kind of garner that national attention and focus if you will that's not too Washington based that I think

probably this and what's in it probably deserves that kind of recognition.

If you are interested in can recommend some folks to talk to you about it.

DR. SHINE: That'd be interesting.

Barbara.

DR. McNEIL: I actually hadn't I'm not sure if I was clear on what I was saying but I wasn't actually recommending a public meeting.

I was assuming that if we can just go as fast as humanly possible to get opinions in the way Peter suggested and the way Norris and Carlos could implement, we would have them.

That's going to give us as broad a spectrum as we can possibly get. Public meetings may add a little bit, but they can also waste a lot of time and add a lot of posturing.

DR. SHINE: We're on the same page, then.

DR. McNEIL: So forget it.

DR. SHINE: We're on the same page. I misunderstood what you are talking about.

Any further comments about this report? Allen?

DR. ROSES: Yes, I'm a little concerned that we are trying to decide what to do with a report, when this is a report essentially to the Commissioner. And the Commissioner is going to need some input I think into what he thinks we ought to be doing with the report.

Second, the fastest way that I know of getting information out is to put it on my daughter's Facebook.

DR. SHINE: Well, Allen, it's true. But it seems to me it would not hurt at all this is already posted on the web if there were an opportunity for people to comment on it, that could be useful to inform the commissioner; I don't see any problem with that.

Any other comments?

We are going to take a break and have a public hearing, but I would like to know if there are are there any individuals who want to speak at a public hearing?

OPEN PUBLIC HEARING

(No audible response)

DR. SHINE: No? Because I don't see the point in taking a break and coming back and announcing that there is no public hearing.

COMMENTS FROM THE SCIENCE BOARD CHAIR

DR. SHINE: Well, let me make in the absence of someone charging the mike, let me make a couple of closing comments.

First of all I want to express my personal appreciation to the staff. That includes Jan and Carlos and Norris from the time that I've been involved with this Scientific Advisory Board. You've provided really important support to the Science Board.

I want to express my appreciation

to the members of the board who have been attentive and participatory at the meetings, but also been available for this project and for consultations; for peer review of project problems that have come along. And I think that input and that participation has been very important.

Janet has been a stalwart participant and informant and giving us heads up on developments and allowing input and so forth, as well as the work that she did on the science review; thank you.

I want to again thank the Commissioner, and I would urge my colleagues on the board to remember that a dozen years ago the Science Board was really very active in terms of looking at science, evaluating programs, things of this sort. And then at least when I came on board, had slipped into what I would call a dog-and-pony show version of the Science Board, where the staff took what they thought was appropriate and

presented it to it, often taking up all the time of the presentation, so there was no opportunity for real discussion and interchange. And I give Commissioner Crawford credit for the fact that he empowered us to have an executive committee that would create an agenda for the Science Board, and then as I've expressed twice today, Commissioner von Eschenbach has really tried to use this Science Board, whether it was on the melamine problem and the consultations there, or the science study or whatever.

But like any other activities in a democracy, I would just urge my colleagues on the Science Board to remember that these opportunities and privileges are not earned easily, and I would hope that we do not lapse back into the dog-and-pony show version, but in fact the active Science Board who has the interests of the agency in mind, and which is pro-active.

Criticism can be painful, but in

fact it can also be useful. And I think as long as we have open dialogue, open discussions and so forth, it can be for the benefit of the agencies, we ought to do that.

To the staff, many of whom attend these meetings, thank you for your input, for your commitment, for the very good work you do for the agency, and not only for the American people but for the world. You are in fact the world leaders, and in spite of our concerns about where the agency is going, I am quite convinced that we continue to have some sterling performers, stressed and overstretched, as the Commissioner said, but meeting responsibilities.

Our pledge, my pledge, is to try to do whatever I can in the private sector to try to see whether we can't move the agenda so that both the programs and the resources required in order to keep the agency the premier agency in the world can happen.

And I know my three colleagues who

are going off the board will assist in this activity.

I can't close without saying to Gail, I'm fond of the wonderful phrase from Guys and Dolls, you have our marker.

Thank you so much, and thank all of your colleagues for a superb job.

ADJOURNMENT

DR. SHINE: If there is no other pressing business, and I see no hands, this meeting is adjourned.

(Whereupon, at 3:32 p.m. the proceeding in the above-entitled matter was adjourned.)