U.S. FOOD AND DRUG ADMINISTRATION

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SCIENCE BOARD ADVISORY COMMITTEE

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MEETING

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THURSDAY,
JUNE 14, 2007

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The meeting convened at 8:00 a.m. at the Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, Maryland, Kenneth I. Shine, M.D., Chair, presiding.

MEMBERS PRESENT:

KENNETH I. SHINE, MD	Chair
GAIL H. CASSELL, PhD	Member
SUSAN KAY HARLANDER, PhD	Member
LONNIE KING, DVM, MPA	Member
DAVID R. PARKINSON, MD	Member
ALLEN D. ROSES, MD	Member
LARRY SASICH, PharmD, MPH, FASHP	Member

FDA STAFF PRESENT:

ANDREW VON ESCHENBACH, MD	Commissioner of Food and Drugs
JANET WOODCOCK, MD	Deputy Commissioner and Chief Medical Officer
DAVID ACHESON, MD	Assistant Commissioner for Food Protection
NORRIS E. ALDERSON, PhD	Associate Commissioner for Science
ROBERT E. BRACKETT, PhD	Director, Center for Food Safety and Applied Nutrition
KATHRYN CARBONE, MD	Associate Director of Research, CBER

STEVEN GALSON, MD, MPH	Director, Center for Drug Evaluation and Research
DAVID HATTAN, PhD	Center for Food Safety and Applied Nutrition
CARLOS PENA, PhD	Committee Executive Secretary
DANIEL SCHULTZ, MD	Director, Center for Devices and Radiological Health
CARL SCIATTANO	Division of Field Science
WILLIAM SLIKKER, Jr., Ph	DDeputy Director for Research, NCTR
STEPHEN SUNDLOF, DVM, PhD	Director, Center for Veterinary Medicine
DOUGLAS C. THROCKMORTON, MD	Deputy Director, CDER
MARLEEN WEKELL, PhD	Director, Office of Research, Center for Veterinary Medicine

ALSO PRESENT:

CAROL MACZKA, PhD	USDA

PUBLIC HEARING PARTICIPANT:

MUKUND PARKHIE, DVM, PhD	Pharmaceutical Regulatory Solutions

A-G-E-N-D-A

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

8:05 a.m.

DR. SHINE: Good morning. Let me convene this meeting of the FDA Science Board Advisory Committee meeting this morning. We will be joined by other members of the committee who are en route. As many of you are aware, the weather has not been salutary for travel over the last day or so, said he who arrived at 1:00 a.m. this morning, but what I would like to do is to briefly go around and have us introduce ourselves to each other and recognize that as the morning goes on we'll add additional folks and we'll have them introduce themselves as possible.

There are two new members of the Science Board. John Linehan, who is an expert in biomedical engineering and medical technology at Stanford has accepted a position on the committee, but he will not be able to join us until the October meeting. But at the far left is the other new member, Larry Sasich, and Larry, perhaps you would introduce yourself? And then why don't we go just go down the table.

DR. SASICH: Thank you very much. Larry Sasich. I'm the Consumer Representative and

I'm presently teaching pharmacy students about the Food and Drug Administration, the process and drug information at the LECOM School of Pharmacy in Erie, Pennsylvania.

DR. SHINE: Thank you. Allen?

DR. ROSES: I'm Allen Roses. I'm the Senior Vice President of pharmacogenetics at GSK and as of today will be transitioning to Duke University.

DR. SHINE: David?

DR. PARKINSON: I'm David Parkinson. I'm Senior Vice President responsible for oncology research and development at Biogen Idec.

DR. KING: Good morning, I'm Lonnie King. I'm the Director of the National Center for Zoonotic, Vectorborne and Enteric Diseases at CDC in Atlanta.

DR. HARLANDER: My name is Susan Harlander. I have a consulting company called Biorational Consultants. Focus is on genetically modified foods and I'm also associated with a little company called BT Safety that looks at bioterrorism, intentional contamination of the food supply.

DR. SHINE: Why don't we skip over to

Carlos here and we'll introduce the commissioner in a moment.

DR. PENA: Carlos Pena, the Executive Secretary to the FDA Science Board.

DR. WOODCOCK: Janet Woodcock, Deputy Commissioner, Chief Medical Officer, FDA.

DR. ALDERSON: Norris Alderson, Associate Commissioner for Science at FDA.

DR. ACHESON: David Acheson, Assistant Commissioner for Food Protection.

DR. BRACKETT: Bob Brackett, Director of the Center for Food Safety and Applied Nutrition.

DR. GALSON: Steve Galson, Director of the Center for Drug Evaluation and Research.

MS. CARBONE: Kathy Carbone, Associate Director for Research, CBER, sitting in for Dr. Goodman, Center Director.

DR. SLIKKER: And Bill Slikker, Director of the National Center for Toxicological Research, FDA.

DR. SHINE: Thank you very much. There are two members of our committee who will not be able to be with us. Barbara McNeil, who is an expert in public policy, has just been named as

the interim dean of the Harvard Medical School so until they get a dean I suspect Barbara's going to be pretty busy at the medical school. And Xavier Pi-Sunyer who as you'll hear in a few minutes has been very active in the melamine work was not able to join us.

Commissioner, we're delighted that you're able to be with us. I do want to indicate to you that we've been very pleased with the interest and willingness of the Science Board to go beyond its semiannual meetings in terms of a variety of kinds of activities, and as you know, later today Gail Cassell will report on the very extensive review of FDA science which you requested and I've had the opportunity to participate both by telephone and in person with that group which is very much engaged, and Gail has assembled a superb group which includes members of the board and a very large number of ad hoc experts from around the country.

I was also very much pleased that Lonnie King who's here chaired a report on NARMS which we're going to review later today. I had a chance to review that and it's really a very well thought out careful evaluation and along with

other members of the board plus ad hoc members they did a very, very serious in-depth review. And finally, when the melamine problem developed, the - we were involved in identifying the peer reviewers for the melamine report which we're going to hear, and I have to tell you, every single individual that I called, asked them to participate in that review, accepted without hesitation. The response that I got from people both on the board and ad hoc participants that the work of the FDA was extremely important was reflected in their willingness to immediately say, even though it was going to be a rush job so to speak, that they were willing to participate. So I'm - I believe the Science Board if anything wants to be more active, more participatory in terms of directions that the agency might take and we look forward to your comments.

COMMISSIONER VON ESCHENBACH: Thank you, Mr. Chairman. I want to apologize to the people who are behind me. I'm a little bit uncomfortable turning my back to you. I don't mean to do that, but I do want to have the opportunity to be able to speak directly face to face to the members of the advisory board. Let me

begin, Mr. Chairman, by first thanking you and thanking all the members of the board, and many of the other individuals that you alluded to that you contacted and asked for help for the work of the Food and Drug Administration. We are enormously grateful for your hard work, your effort and your contributions in helping to guide, helping to advise, helping to provide the necessary inputs so that FDA can be what we discussed we had to be when we first came together almost 20 months ago. We talked then about a vision in which not only would FDA continue to be a science-based regulatory agency, but even more importantly that we became a science-led regulatory agency. And the nuance there being that we recognize on the Science Board the fact that we are in the midst of a virtual revolution in science and technology that is providing for us new tools, new opportunities, new ways of being able to perceive and understand the problems and the issues that FDA must confront. And we therefore needed to be very proactive in bringing science to the fore within the agency and use it in a way that would in fact illuminate the pathway forward, would in fact guide us and direct us with regard to what

FDA must be doing in the future, in tomorrow.

And you're going to hear in just a short period of time from Janet Woodcock who really has been exceptionally gracious in accepting one more burden, one more responsibility in her long career at FDA, and that was to truly focus her effort, her leadership on this concept of FDA being science-based and science-led, and in her role as deputy director and role as chief medical officer to really take responsibility for our scientific portfolio and its integration and its coordination and its ability to actually serve as the foundation for everything that we will be doing as a regulatory agency, and this integration of science and our regulatory process being a seamless interface. Janet has worked extremely hard in many initiatives in an effort to begin to implement this in a much more active way, one of which is of course to emphasize many of the components that are contained within our Critical Path opportunities. I am going to turn over the meeting to her on my behalf because I have to do the other part of that job, the other part of that responsibility which will be to leave here and go directly to Capitol Hill where I'll spend the

entire day engaged in discussions and in conversations about the need for support for those kinds of initiatives so that we in fact can be the FDA that this nation deserves and FDA that this nation expects and even in fact demands.

And so in the time that I'm going to have with you this morning I'm not going to focus on many of those scientific and programmatic issues and leave that to Janet. But rather, let me take my time with you to just basically discuss the state of the FDA and to have an opportunity to engage even in more of a dialogue with you in terms of responding to your questions and responding to many of the issues that you are concerned about.

I think the simplest and best way for me to describe the state of the FDA today is to say that it is stretched and stressed, and that is a candid assessment of the fact that it's an agency whose portfolio of responsibilities continues to increase in their scale and scope, continues to increase in the complexity of the problems that we have to address and face, and you will be looking at one very small part of that portfolio. As major as it has been, it is in fact

still a small part of all of the things that are going on at FDA, and that is in fact the response to the recognition of the fact that there were animals who were dying as a result of consumption of pet food, and then the detective story that went into that in terms of being able to identify that problem, trace it back to its source and then that resulted in a very significant effort and undertaking with regard to our ability to address melamine contamination in our feed supply.

Those kinds of day to day responsibilities and activities in the context of an agency that is in fact limited with regard to its resources has really set the stage for what has currently been a major emphasis on our part, that is to work very effectively with Congress and with the Administration to rebuild and to expand that resource base. And you are aware that in the `07 budget we had significant increases to bring us back on a positive trajectory, we are anticipating as we speak an outcome of the `08 budget that would in fact continue to increase that trajectory of growth, and most importantly as we speak we are engaged in the preparation of the `09 Administration's budget and the development of

that and that is done in a way to continuously increase this trajectory so that we can bring to the agency the kind of resources that are necessary to address the demands and the expectations.

With regard to stress, the fact of the matter is that we are engaged as we speak in a very, very active legislative session with regard to the FDA. It is a session in which on one hand because of the reauthorization of our PDUFA and MDUFMA acts and other pieces of important legislation like PREA, we are engaged in a great deal of legislative activity, and that in addition to the development of bills that are particularly affecting FDA, it is also a period of time in which there has been a great deal of attention to congressional oversight with regard to the FDA. And so as of mid-May this current Congress has held or scheduled 19 hearings that were involving FDA as its primary witnesses. We've had 22 document requests that are addressing very complex issues and that requires a great deal of attention on the part of the agency to be appropriately responsive, and there have been 505 letters with regard to our response to Congress. I have had

the opportunity to appear on multiple occasions before various committees on the Hill and you're much aware of their great concerns with regard to the issue of safety. And so we are approaching these issues on a very broad front to provide comprehensive plans that will address the agency's science-based and science-led response to the need to continue to be sure that we have an efficient and effective pathway that allows for rapid and seamless ability to regulate drugs and applications that come to us, drugs, biologics and devices, so that we can bring to the American people lifesaving and life-enhancing solutions while at the same time making certain that we are addressing the issues related to risk, and the science of safety is as important to us as we go forward in that regard as our ability to use science to define efficacy.

And at the same time to recognize that within that safety context we're not just looking at medical products, but also the very important role that food plays in that continuum. And in addition to our continuous attention to food as it relates to its role in nutrition is to really emphasize our responsibility to address food as it

relates to its safety. And that has been an extremely important trans-agency effort that has taken on multiple aspects that I think that the board is aware of and will continue to be engaged in.

With regard to that effort one of the important initiatives of recent implementation is to take the experience that we had with pandemic almost two years ago when it was in fact a major issue that needed FDA's attention and look at it from the perspective of creating the FDA Pandemic Task Force that in fact created the Pandemic Strategic Plan for the Food and Drug Administration that we released in March. That plan gave us an opportunity to work across the entire agency and bring the centers and bring all of the elements of the agency together into an integrated, coordinated effort. We are attempting to do that same thing with regard to our approach to food, and to see food defense and food safety as integrally related, and create a trans-agency effort to address food protection. David Acheson has taken the responsibility to head up that effort and it is bringing into play the incredible strengths and resources of components of the FDA

like CFSAM and CVM along with all of the rest of the agency. And we believe that that will help us as we move forward in presenting to both the Congress as well as to the Administration and to the public an understanding of FDA's comprehensive, multidisciplinary and integrated approaches to addressing many of these problems and challenges.

As we go forward we will - over the next year I will be particularly focused on two areas that I will make my highest priorities from the perspective of the commissioner. You know that when I first arrived I chose five strategic objectives in terms of how I might best serve the agency. As we go forward over this next year, the two areas that I will focus on primarily will be in the area of workforce development and that will include not only our continued expansion of our workforce as related to many of the issues I alluded to with regard to appropriations, but also the development of that workforce and Dr. Woodcock will be addressing one particular aspect of that, namely our fellowship program. But we will also be addressing career development and the nurturing of our professionals within our workforce, and

especially as it relates to our culture and our work environment as it relates to addressing issues of morale and the ability to create an environment that welcomes diversity, especially diversity of thought and allows for open, vigorous academic debate and discussion of the various aspects of our regulatory decision-making process and arrives at a FDA decision and process.

In addition to that kind of address or infrastructure issue of culture, it is also extremely important that we look at process. And so in addition to workforce development over this next year I will be communicating with you along with others in terms of our efforts at process improvement. There is much that we are doing within the Office of the Commissioner to help lead and organize that effort, but we are addressing it from the perspective of creating opportunities for us to have efficiency and effectiveness in the regulatory process that also is able to then provide transparency, openness and predictability to the stakeholders who are critically dependent upon the FDA to provide the decision-making processes that will truly lead to protecting and promoting their health. We have many challenges,

Mr. Chairman, but at the same time the opportunities are even more enormous and exciting in their scale and scope, and we are committed and fully prepared with the support of the Science Advisory Board to continue to address those opportunities as a science-led agency as well as a science-based agency. And with that I'd rather take questions and answers and perhaps a dialogue.

DR. SHINE: Thank you, Commissioner. I appreciate very much your comments. I should perhaps - a comment that your emphasis on career development resonates closely with some of the discussions of our ad hoc review panel in science which has pointed out in its deliberations that for those employees of the agency who are involved in research of one kind or another, that the ability for them to get to meetings to be able to learn new techniques, either with other agencies or at other institutions and so forth, has in the minds of many of the reviewers been somewhat limited by resources and so forth. And I think you will see some fairly strong recommendations with regard to the necessity for career development for scientists within the agency as a very high priority if the agency is in fact going

to be able to have a workforce that's on the cutting edge of whatever the science requires for their regulatory sessions.

I do have some questions, but let me turn things over to the committee first and see what other questions you want to make. Susan, do you want to make any comments about food safety?

DR. HARLANDER: Will we have an upcoming opportunity to review in more detail what David is planning? Or can we ask for any additional details on that?

COMMISSIONER VON ESCHENBACH: No, we very much look forward to that. David has been leading a planning effort to really bring together all the parts and pieces of what we can do as an agency to address food protection and to recognize it from the perspective of we, as across our entire continuum, are approaching a lifecycle - product lifecycle approach to things. So for example, whether it's drugs or food, we're viewing our ability to be engaged from the very beginning of production all the way to the delivery and consumption end of the equation. So David is taking that concept of lifecycle from production to consumption and also approaching it from the

point of view of domestic as well as imported sources of food and beginning to structure, and lay out a strategic plan that would enable us to assure the protection of that entire chain, and do that on a risk-based model that borrows from experiences that we've had that CFSAM has pioneered and headed up and will be announcing for example using risk-based model assessment, like Carver models, et cetera. So that's all work in progress. It builds and simply helps to coordinate and integrate the strengths and the activities that are occurring in individual centers, and that coordinated effort we will be promulgating once it is finalized and developed - no, finalized, but at least the proposal has reached the point of maturity where we believe then we can welcome comment on it.

DR. SHINE: Lonnie? Questions?

DR. KING: Thanks very much Commissioner for those comments. I'm taken on how much they are similar to some other federal agencies, CDC in particular, and it comes with as you said you know, expectations and demands of the public on how we operate. Could you just maybe talk a short time on your plans on you know, kind

of what we call silo-busting. You've got, you know this as kind of an internal focus for the next year. What are you doing to kind of - this meta-leadership idea of pulling the centers together in a coordinated way? And the second part of that would be coordination with other agencies outside of FDA.

COMMISSIONER VON ESCHENBACH: Well, there are a couple of very important aspects that I'm looking forward to over the next year, one of which essentially starts from the top down. We've made some changes for example in how we are managing our daily meetings in a way that enables me to bring the deputy commissioners together with the center directors, the operational leaders. We meet every morning now at 8 o'clock with the idea that it is no longer just morning report in which we are defining what the issues of the day are, but more importantly discussing and defining what the issues of tomorrow are and what our strategic direction has to be. These are opportunities for us to really begin to work across the various if you will compartments or silos, much more horizontal integration as people continue to carry out their vertical line responsibilities. That

along with some of the things that are occurring with regard to the culture and process improvement activities which will be again crosscutting and require that collaborative interactive process.

We're looking at some opportunities for example even in the way in which White Oak the new home for a large portion of the FDA is being constructed as to create a campus that's an integrated campus, and even defining ways in which we will drive, promote and support more interaction across the various disciplines and much more sharing. One of the most important contributions to that is the work of this committee in the assessment of FDA's scientific portfolio in which you've been working with Norris so closely on because the expectation is that we will begin to see science across the agency as not occurring in silos, but rather occurring across the agency in a coordinated and integrated way. So it's leadership, it's structure and it's function, and across those three areas the concept is always to look for coordination, integration and sharing while at the same time emphasizing and supporting individual excellence.

DR. SHINE: In that regard I think

again, one of the areas that's been under intense discussion is the notion that - and the commissioner has been engaged in some of these conversations, the space at White Oak shouldn't be simply given to individual silos, but the space ought to be created for program which involves participants from multiple agencies, and that's a challenging issue, but it is one of the strategies which could physically bring people together from a variety of portions of the agency around problems as opposed to around the organization pieces. David?

DR. SASICH: It's Larry.

DR. SHINE: Okay, Larry.

DR. SASICH: Thank you very much Commissioner, just a couple of things. The first one is I think we're very pleased to see that there is now a risk communication advisory committee that's been announced. Do you at some point in the future see a research function for the Food and Drug Administration in say the social science of communicating risk to the public, either conducting its own research, or funding research?

COMMISSIONER VON ESCHENBACH: Well, I

would be very emphatic in the affirmative with regard to the importance of research as it relates to risk communication. The role that FDA should play with regard to that research I think is something that needs to be discussed and deliberated, but the fact that research has to be integrated into our functionality as it relates to risk communication is absolutely essential. There are bodies of knowledge being developed with regard to risk communication now using functional imaging as people cognitively process messages that are coming to them, and how the format of those messages might change in a way that alters or changes their perception, understanding and processing. That kind of research is critical if we're going to be able to fully appreciate and understand how we should be sharing with the public information that they need to have in order to make informed decisions about their own healthcare. And I think that's a responsibility that FDA has and that's a perfect example of where we must be a science-led as well as science-based. Science-led in that we should be embracing seeking out and finding that research that's illuminating that new pathway. How much of it we

should be doing on our own, how much of it we should be supporting and nurturing that's being done elsewhere and how much we should be integrating and collaborating with others is I think something that we have to work out operationally. But there's no question it has to be a part of our portfolio.

DR. SASICH: Great. Thank you very much.

DR. SHINE: David?

DR. PARKINSON: Comments on how this process improvement will link with the activities of other federal agencies, or within - or external entities, for that matter?

COMMISSIONER VON ESCHENBACH: Well, it's not linked necessarily outside of the agency at this point, David. It's more of an internal function and it begins with the senior leadership of the FDA. The deputy commissioners are collectively addressing this because each has a part and a place in this effort. We've created the Office of Integrity and Accountability and one of the immediate activities that's occurring there is a coordination between Bill McGonagah who's heading that up on detail at this point and

Georgia Coffey to address issues of culture and intellectual diversity and the climate that supports and nurtures that.

And then as far as process is concerned, for example one of the processes we are immediately looking at as a model system for process improvement is the process of issuing of guidances. And so how we go about that process, how we compartmentalize and look for process improvement is something that's getting immediate attention. Randy Lutter as the Deputy Commissioner for Policy has been addressing the guidance issue, but it's something that everyone's participating in, including the Chief Operating Officer John Dyer. Janet's playing an important role because of the functionality of guidances if you will.

So to give you a perspective, we're going to be breaking down the portfolio, looking at what are critical processes. As we think of the agency as simply a data management organization, information, data, comes in in the form of an application or in a variety of packages. We acquire, we assemble, we analyze, we assimilate that analysis and we act, and that

involves a process and we need to be looking at that process in a way that provides much more of an understanding, a predictability, a transparency and an ongoing effort of efficiency. And the only way you can do that is to first define it, map it, lay it out and then start looking at where you have critical points in that process that you could begin to provide opportunities for improvement. One of the really interesting, exciting ideas around this is how much we can do with regard to best practice within the agency because as centers have gone about their own regulatory process, whether it's in CDER or in CBER or CDRH, wherever, they have defined process and they have opportunities now I think to cross-share best practices in a way that improves the system and the outputs.

DR. SHINE: We have just a couple of more minutes. Allen, do you have a question?

DR. ROSES: Having spent a lot of time in the science review and reading the newspapers, the question is sort of more of interest. When you spend this time on the Hill, is there a wealth of support for going forward with the kinds of things that need to be done, or does the few, the

loud and the arrogant control the agenda?

COMMISSIONER VON ESCHENBACH: Well as you might expect, Congress is a lot like society, it's very heterogenous and there are different levels of conversation that are occurring. There are those who are focused primarily on the problems and wanting to understand the issues and the perceived problems. There are others who are focused on solutions and want to address what needs to be done and what can be done and when it can be done and so it really takes on a variety of discussions. But at the end of the day what has been very obvious to me and I think hopefully is apparent, is this uniform recognition of the criticality of the FDA. There is no problem with people understanding the essential critical role that FDA is playing in protecting and promoting the health of this nation. Senator Kennedy has gone so far as to state openly in hearings that it is the most important agency in healthcare in this country today.

Second, there is no longer any doubt in people's minds that it's an agency that needs support and an agency that must be nurtured if it is in fact going to be responsible. So those two

pieces of the story are critically important and those are I think now no longer at issue. The issues now are what will you do and what will that affect. Activities are not the issue. What will you actually affect in the way of change and in the way of improvement and the way of better outcomes, and then what resources are required to do that and justification for those. So that's the way this is evolving. It's a way of essentially presenting to them both a strategic plan and a business plan. What has to be done to get the kind of outcomes that you want and what will be the investment required on the part of the American people if that outcome is to be achieved.

DR. SHINE: Commissioner, we know that you're on a tight schedule. I just want to call your attention to one concern that some of us have and recognizing we're going to perhaps have opportunities to talk about it later in the day. I think there are a number of us on the board who are still concerned about the methodology for post-surveillance safety and particularly the central role of the very important committee that was put together to oversee this which consists of essentially all government employees from multiple

agencies. We've had conversations at these meetings before about the way in which decisions are made in that body. We've had discussions about the FACA issues with regard to how you involve non-government employees and other consultants in the workings of that activity as opposed to sort of advice from a distance. The board still is interested in solutions which might involve either a subcommittee of this board or some other mechanism by which non-governmental individuals can participate in the deliberations of that process in terms of how and in what way decisions are made about potential problems with drugs after approval. I don't think it's fair to ask you for a solution to any of those things right at this time, but I do want you to be aware that this is a continuing concern of the board in terms of that process.

COMMISSIONER VON ESCHENBACH: Janet, comment?

DR. WOODCOCK: Yes, I think maybe the board could perhaps propose some alternatives because as you know there's tremendous concern about conflict of interest of any outside advisors, especially in situations where we're

making a decision about a regulated product, okay. So that means that any outside constituted board has to go through a very rigorous vetting process for conflict of interest, and that is the reason why the Drug Safety Oversight Board is composed of federal employees who do not have the same you know concerns about conflict of interest. So we already have a committee. There is an FDA committee for drug risk management that is a FACA committee, a regularly constituted advisory committee. So how to go beyond that, you need something more nimble and agile, something that can be convened quickly in the situation where you're considering a risk problem, a safety problem with a drug. However, at the same time if you're going to have outside members then you have to go through an open process of conflict of interest vetting. So that's the situation we find ourselves in. I think we would welcome any input from the committee on how - on additional ways to have outside input.

COMMISSIONER VON ESCHENBACH: Let me also add to that if I can that I want to go back to the concept I put before you before which was this total lifecycle approach. It's important for

us to look at this issue, whether it's drugs, or biologics, or food, or whatever is to first of all, FDA playing a much more proactive role on the front end to build quality in. And part of what is extremely important about the effort that you've been engaged in and why this Critical Path initiative is so important is because there are many pieces of Critical Path that are addressing just that, how do we build quality in on the front end. How do we create a science of safety so that we're understanding safety as well as efficacy at a molecular level if you will, or functional level.

In addition to building quality in the front end, the second part of that is after a decision is made how do we stay engaged in that lifecycle of that product after it's out on the marketplace so that we recognize that delivery is in fact a discovery platform. There is still much to learn about that particular drug as it's being used in a diverse population which we would never be able to learn in a clinical trial of a subset. So that we need to begin to look at that as a platform and as a part of the system, begin to think and really work through what does that need

to be like with regard to information technology infrastructure, with regard to the kind of data we would be accessing and where those analyses would occur, on and on and on. It's not just a matter of do we have the right committee to provide advice or input, it's do we have the right system to get us the right information in the right way at the right time upon which then make a decision about that particular product as it is being utilized in a post-market setting. So I think the problem, the issues are much more complex than just simply adjusting or changing an advisory committee or an oversight committee. I think it's changing the whole construct upon which this data is being acquired and how we then are able to act upon that data.

DR. SHINE: Commissioner, I don't think that any of us would argue with that notion. The question becomes, and I think at least I'll consult with other folks on the committee, I think we'll accept Janet's invitation. Looking as broadly at those sets of issues with as much sophistication as possible from as broad a perspective as possible we think could also be valuable in terms of how the overall system works,

and I think that all we're interested in is the notion that both the perception and reality that it's an open enough process so that we can do it well. We know that you have to get off to the Hill.

COMMISSIONER VON ESCHENBACH: Yes.

DR. SHINE: In the interest of time, quick.

COMMISSIONER VON ESCHENBACH: Yes.

DR. HARLANDER: As you consider this total lifecycle approach which I totally agree with you on, I think at the very end of that is going to be managing consumers' perception of risk when it comes to both food safety as well as drug safety. And I would just encourage you to include that piece because we can never ensure, no matter what process we put in place, you know total and complete safety for every single person in the food supply or in the drug supply, and so there is always going to be some of that risk and managing that and communicating about that to the public I think is a critical piece as well.

COMMISSIONER VON ESCHENBACH: Well, I could not agree with you more and I think it points out the issue of where committees if you

will or where a collection of individuals from outside of the FDA could be an extremely part of contributing to and supporting the FDA in this regard. The kind of committee or a collection of people that the chairman just alluded to I think needs to be convened around this discussion of risk and a risk doctrine. It's a societal question and it has a whole host of ramifications, including legal ramifications as well and we as a society have to define what we're talking about when we're talking about risk and benefit and expectations in that regard. Because if we don't frame that, if we don't have that framework the decisions that FDA makes are going to be occurring in a vacuum and that will not - but that's a discussion that I think needs to be much broader than FDA. I think that's a societal discussion that should bring you know key leaders from all sectors and segments of society, private as well as public and much the same complexion that the chairman just alluded to.

DR. SHINE: Commissioner, thank you very, very much. We appreciate your leadership, your communications and *vaya con Dios*.

COMMISSIONER VON ESCHENBACH: *Gracias,*

senor. Thank you, Mr. Chairman. Again, thank the committee on behalf of - I thank you on behalf of all of the FDA for the critical important contributions. It's been a great source of strength and comfort if you will that as we've gone through many of these challenges of late we've had the opportunity to know that we could turn to you and ask for your help and you would in fact be there for us. And whether it's a risk assessment, melamine, or being able to look at our scientific portfolio. In the period of time I've had the privilege to be here I haven't asked the Science Board to do one thing that you haven't immediately responded and responded with enthusiasm, and that source of support means a great deal to us and I thank you for it.

DR. SHINE: Thank you and thank you for your leadership, Mr. Commissioner. Carlos, tell us what we can do today.

DR. PENA: 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 this 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 bioinformatics initiative and fellowship program. The Science Board will hear about and review the agency's Interim Melamine and Analogues Safety/Risk Assessment. The Science Board will then continue their discussion of the review of both the agency's science programs and the National Antimicrobial Resistance Monitoring System, NARMS program from the March 31, 2006, Science Board meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants it has been determined that all interests in firms regulated by the Food and Drug Administration present no potential for an appearance of a conflict of interest at this meeting. In the event that discussions involve any other products or firms not already on the agenda for which a 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.

We have two public comment periods scheduled for approximately 10:45 and 3:15 p.m. I would just remind everyone to turn your

microphones on when you speak so that the transcriber can pick everything up and turn them off so that other people can speak following you. Thank you.

DR. SHINE: Thank you, Carlos. With that let's go to our agenda and we're very pleased that Janet Woodcock who's Deputy Commissioner and Chief Medical Officer is going to give us an update about bioinformatics and the FDA Fellowship Program which fits into the career development workforce issues which the commissioner addressed. Dr. Woodcock?

DR. WOODCOCK: Thank you and good morning. Before I start on that I want to respond further to a question that Larry Sasich asked about risk communication and the science of risk communication. That's actually one of the questions we've asked the Science Review Board or subcommittee or whatever they're called and we have specifically asked what research needs are going to occur in that area, what scientific disciplines and knowledge we need access to. We're completely aware that the whole social science piece is an area where FDA does not have the strength that we need and we have not - we do

not really have access to resources we need. And it gets back to the question of risk perception and so forth. We recognize that's a whole area that there has to be much more robust communication. Actually, we've recognized that for a long time, but we have not achieved probably a very good ability to access that science.

I was asked to talk about - can you hear me? Okay, I'll just stay away from this microphone. I was asked to talk about two things this morning. First of all, the FDA Fellowship Program that we're planning to put into place and second of all our informatics efforts. Can I have the next slide? I'm sorry, Carlos. Okay, the next one after that. Bioinformatics, okay. Let's start with the Fellowship Program. Now currently FDA has active programs with fellows. A large variety of fellows come to the FDA. As a cross agency we bring in people in the scientific area. We also bring in presidential management interns and others into our program in the administrative side, and we have over - more than several hundred actually trainees at the FDA at any given time such as now. These programs right now are administered by the centers and the recruitment

and so forth is all done by the centers.

So what we would like to do - could I have the next - we're planning to do is to have next year a fellowship program that is a cross-agency program. And this program we hope would be administered it's possible by the foundation that's being contemplated by Congress right now. Of course that's just pending legislation so that may or may not come about. If not, we might be able to go through other foundations, external foundations that exist. The problem this year, of course this is a very short funding year for the FDA. We did not have dollars to set up a larger program this year, but we have put all the building blocks in place for a larger fellowship program. What we are contemplating doing, and this will help when we get the report from the science subcommittee, it will help us to target specific areas of need and we can then have centers nominate areas where they would like to have fellows with specific expertise and training. I don't think I'm doing this.

DR. PARKINSON: Janet, do you have a Blackberry?

DR. WOODCOCK: No, not on me I don't.

DR. PARKINSON: Okay. Usually that's the culprit.

DR. WOODCOCK: Yes. It might be - if you look beside where I'm sitting. I don't have electronic stuff on me at all. All right, thank you. So what we're contemplating is that the centers would nominate areas. Some of those would be identified by the science review. That seems much better, thank you. For example, obviously we would like to get some fellows who are expert in communication and social sciences related to that into the agency and help to build our programs in that area. There is a lot of research that needs to be done for example to guide regulation in the area of advertising regulation, in the area of our risk communications around food outbreaks and so forth and so on.

We also hope that, and we have heard from a number of outside parties who would be willing to establish fellowships for the FDA with some third party non-profit, through a foundation and you know fund one or two fellows to come in. And these are you know professional societies, non-profit organizations and even perhaps industry. We're contemplating a 2-year duration

of fellowship. That is what we have right now for many of our fellowship programs. What we will do with this FDA-wide fellowship though is have a formal program with didactic training in things such as food and drug law, the operations of the FDA, regulatory policy and so forth so the fellows are not just exposed to the science in their particular area, but get a good overview of the FDA and actually the sort of executive branch program that they're embedded in and how that works. But the fellows we are contemplating, very similar to what we do now, that the fellows come in and perform regulatory activities. This is really on-the-job type of training because there is no other place really in the world that you can learn about how to do regulation except maybe in another regulatory agency around the world. So the fellows would be engaged in either research laboratories, doing research or testing, or engaged within the review programs, actually participating in review. Next one.

So the expectations that we have, and why this is very important and it's part of what you heard from the Commissioner, the sort of whole development program he has for the agency. We

want to get in recently trained scientists and clinicians and expose them to FDA regulatory science and learn what it's all about because I think as you all know, most people do not know what this type of science is about and many of us who have come and done this sort of science find it's extremely interesting. Actually it's an intersection of science and law and policy in a way that you really don't see many other places. And we think they will learn all this, these fellows coming through, but we will benefit also from people who've had recent training, who've been out in the clinical world or out in the science labs around the country that will benefit us from their knowledge as well. And what we've found in the past with the small fellowship programs we have which are not at the scale we're actually contemplating here is that when we do get people in, some outstanding scientists will actually decide to stay and make a career at the agency. This would be a small percentage because most people really don't you know want to do this sort of work, but there is a group of people who really find this work fascinating and will wish to stay and participate. Those who don't stay we

think will help serve as ambassadors to academia. If they go out to industry they will actually know and understand the agency and its procedures and its requirements and standards, and that is very helpful when that happens, and health professional organizations, and even the rest of government where we have ex-FDA'ers who are in the Department of Defense and they're here and there throughout the government. Those are very good contacts for us and we think this is a very good type of program.

We also contemplate, and particularly CDRH has done this, bringing in very senior people who are in sabbaticals, or perhaps some of you may remember Don Stanski who was the Chairman of Anesthesia at Stanford came to FDA for several years. It's a very enriching opportunity I think for both parties. So we would also expand that program. And then just equally as important, and I'd be interested in the Science Board's take on this, we really would see this as a two-way street. We can't just bring in people and offer them a great training program. We need to offer as part of this effort training for our scientists. And of course the biggest barrier for

that has been the workload here at the FDA and the reluctance of our staff to send people out because then there's nobody left to do the work, okay. So, but as Dr. Von Eschenbach said, we hope to receive additional funding that would help us run our baseline programs and really the goal must be I think for us to have enough resources that our people can stay up to date, and that means in many cases sending them out either for brief short-term training, or in some cases you know longer programs. And we have done this in the past and it's very successful. Not only do our people gain knowledge and insight, but they also serve as our ambassadors and they're able to teach in the universities and so forth where they go and help people understand what the FDA does. Next slide.

So our plan is we have all the sort of paperwork and training manuals and everything put in place. We hope to have a robust FDA-wide program in place by next year, but again this will require that we are able to get some funding and we identify a foundation and so forth to site this at. And we will target areas first of emerging science, or areas that are hard to recruit in. For example, getting imaging doctors, clinical

doctors who do medical imaging is very difficult. We maybe could get some through a program like this. Nanotechnology, other areas such as data mining and I think is what Larry brought up, risk communication, social sciences. As I said, we recognize we're weak in that area. So, but we would have a portfolio probably of areas of emerging science or we need additional people that would be pretty long and I expect from the subcommittee review we'll be hearing a longer list. So that is what we're going to do under the fellowship program. Do you want to stop there and have questions?

DR. SHINE: For just a moment, Janet. This is really exciting, important. I think you're going to find that the science review group is going to be very enthusiastic. They've been discussing exactly the need for exactly what you're talking about and as you point out, to a certain extent it's a resource issue and whether people will have opportunities to develop additional skills, that is the FDA staff developing skills elsewhere and vice versa. I can think of a couple of very key people in the agency right now who started if you will as fellows, or

as visiting scientists and who decided to stay, including one of your most important division directors. So I can't help but believe that the board would be very enthusiastic about this and would try to be as helpful as it could as you go forward. Any other comments? Yes, please.

DR. SASICH: I think the fellowship idea is wonderful, and I hope maybe we could get together and kind of broaden it to a broader base of say health professional students, the public. I think there is a big misunderstanding about what the agency does amongst the health professions. I think in Archives of Internal Medicine last month, 75 percent of post-graduate medical residents thought that dietary supplements were regulated by the Food and Drug Administration. I don't think many physicians realize that pharmacy-compounded drugs are not approved for any use by the Food and Drug Administration. There's just a big misunderstanding or lack of knowledge of the history of the agency and why we have the regulations that we do, and I hope we can come up with some ways to broaden public understanding in that area.

DR. WOODCOCK: If I could respond to

that, of course I totally agree with you. What you say is absolutely correct and I would hope that as we set up this infrastructure we can work for example with the professional societies, for example with the deans of the schools of pharmacy. Okay, there is a great group of people actually and people we could work with to integrate them into this program in some way so that we have more exchange, the deans of the schools of medicine if they're not too busy, and so forth and so on. So we're not at all excluding any professional group. In fact, we want that. We're starting out though with this identified fellowship program.

DR. SHINE: And I think it's also clear that the science review will include, as you already made reference to, research in risk communication and certain behavioral aspects. That again is a relevant place for two-way exchange so I don't think this is meant to be only molecular biology. It's a very broad. Well, thank you. That's a very good report. Why don't you talk to us about the bioinformatics.

DR. WOODCOCK: Certainly. And when we have their materials finalized we'll circulate them to the board so that you can see what they

actually look like.

All right. This - the next slide, please. Thank you. I'm going to update you on our automation and bioinformatics strategy. And let me say at the outset this is very difficult to communicate. I need a - none of us, we know what we're doing, but it's very hard, it's one of those things it's very hard to tell people about, so please ask questions. And the bottom line here is that we as an agency are getting a grip on this. We have determined our automation needs and our scientific computing needs so to speak. We are developing collectively, all of us together the plan to address these. We are starting to build the systems. We are working in partnership with other agencies and with the outside world. That's sort of the bottom line. But when you get down in the details it is extremely confusing and I'm sorry, but let me do the best I can.

As you all have heard over the years, FDA data management needs are extremely challenging. As the commissioner said, we are really an information management agency. We get all this data in from all these sources, you're going to hear about some of them today, and there

are massive amounts of data that are generated, both surveillance data, data from clinical trials, scientific data, microarray data and so forth and we have to make sense of all these data. It's very difficult to utilize these systematically. Most of the data sources have been in paper over the years, or they might be in a database somewhere, but those databases aren't linked to other databases and so forth.

So we are implementing a multifaceted improvement strategy. Each of the product areas, the people who regulate in each product area have been working on this over the years. What we're trying to do now is bring this all together, have a collective, unified approach to all these data management challenges and process automation. Because part of it is we get in all this stuff and we need to run an automated process to evaluate it. Next slide.

The examples of the problems we have right now, we have very limited access to the data. And you may hear from David, I don't know whether you're going to talk about this, David, but you know our data on movement of regulated products through commerce for example is limited.

Our ability to access data and understand that, our ability to understand what's moving in imports, imported into this country is limited. It's not well automated for various reasons. Our marketing applications we get for all the regulated products is still paper in many cases, all right. And if they aren't paper, they're in often more unstructured electronic documents that cannot be analyzed across files. Adverse event reports or consumer complaints such as about pet food and so forth, these will be received often in paper form, all right. Data standards. Even if we get stuff electronically, if the data are not standardized, then doing analysis on it is very challenging. And so is it widespread adoption or use of good information exchange standards, which are the standards whereby you just send - the protocols that you send things back and forth with, or the terminology about content itself. And then to interface the data when we have the data, our analytic review tools are outdated in many cases. For example, in the post-market area we obviously have to update our analytic tools. Tools for safety signal detection are not adequate and we lack tools for cross-product analyses. In

other words, going outside of one database and pulling other databases together to do an analysis. Next slide.

So what we've decided to do with all these problems that we have is put additional resources in it. Additional resources are being put in this year by the commissioner for the infrastructure, to get our IT infrastructure repaired because it was failing, and human capital. But we are going to have to do changes in regulations, we have been doing these over the years, to move toward a paperless environment. We had a Part 15 hearing several months ago about what will it take for FDA, for all the regulated products and all their required submissions to move to an all-electronic process. And the reason to do this is not just for our administrative convenience, it's so we can protect public health better because we just - it's very difficult to do when all this information is scattered around in paper.

We have developed a strategy for governance planning and implementation I'm going to present to you. We need to be transparent about this. We will add new projects - we're

developing project plans for all this and we're going to add, implement new projects as resources become available. We're developing in the IT world which is a science in itself something called service-oriented architecture where you build modular pieces instead of whole computer systems and then these services can be plugged in across many different applications. And we're partnering with a lot of federal and outside organizations and you'll be hearing more about new partnerships that are going to be implemented in probably the next few months, but right now we have significant partnerships with NIH, with AHRQ who's helped us greatly with things such as our medication terminology and other things that we've had to do, you know the data standards. Department of Defense and the VA we've partnered with again on medication terminology and other things, and then public-private partnerships to help us. Next one.

So the structure we've set up, and I'm sorry, some of this is a little bit administrative and maybe not that interesting, but you need to know about this. In February we set up the Bioinformatics Board, February of `06, to achieve

the agency's goal to get this modern infrastructure, integrated across the FDA approach to informatics. And we've been, since that time we have been implementing this Bioinformatics Board and its sub-boards. Could I have the next slide? Now, people have asked us why do you use the term "bioinformatics?" Well, we use that to describe what we do at the FDA and it was very helpful, Dr. Shine. In the subcommittee review we've had folks, there's an IT subcommittee and actually just interacting with them has been very helpful. And they have talked to us about what they call the information supply chain and that this is all - which we really feel very strong this is all one big piece. So whatever data you're picking up out in the country, say in antibiotic resistance or whatever, there's a supply chain of that information that comes all the way through to making a scientific decision maybe about gene expression profiles and so forth, so it all is of a piece. So that's why we call this all bioinformatics, if you follow me. The FDA business of public health protection involves all these pieces, the regulatory decision-making for all the products that we have. And so that

might involve import data along with gene fingerprints is how we make that decision. So it's all part in our minds of the information supply chain. So the Bioinformatics Board coordinates and oversees all these activities, our business automation planning, the types of things I've been talking about. How are we going to automate our processes to get electronic submission, electronic input databases that we all can access and then the all-important and somewhat you know neglected up to this point export of that data and communicating it to the people who need to have it in a very timely fashion. Next one.

So the real business end of the Bioinformatics Board is what we call the Business Review Board. And we've gotten everybody from the agency who works on a specific process together on this Business Review Board. We call it a strategic business area or whatever. And they are in charge of making the plan basically for how to automate that area across the agency. And they've all been working very hard on this. And if - I'll show you the next slide, it's kind of - next one, please. You can't really see this very well. The members of the board have hard copies of this, but

what it shows is we have really four right now Business Review Boards. One is pre-market, one is product quality which means all the things that go into making sure the products are of high quality, the manufacturing, the inspections, that whole process. That's really to some extent the foundation of what the FDA does. Another board is post-market safety. That has to do with the adverse events and consumer complaints, and all that sort of thing and that board has worked together. And then there's an administrative board. Next one.

And each one of those that diagram shows has its own policy component, its own business process analysis component and all the different things that are needed to analyze what we need to do to get where we want to go. So the Business Review Boards make up project teams then to do the projects under them. And I think I'll talk - the initial project that we have finished planning and we're implementing right now comes out of the Post-market Business Review Board and that project is called MedWatch Plus. And MedWatch Plus, the first project we're doing under that is to implement an agency-wide - a way you

can file adverse events on the internet to the FDA or consumer complaints or whatever it might be, you'll be able to do all those things. And we're working with NIH on this project because they have a need for their investigators to file adverse events as well. And we'll be announcing the details of this soon, but this is - and then following MedWatch Plus we'll be talking about the databases needed to store the adverse events, right, and how we can unify that across the FDA. Not have a single database, but unify the kind of database that we have so we can do cross-analyses and adopt common tools. And that is enabled by the fact that we already have a data standard called the ICSR, Individual Case Safety Report, and that report has been adopted for all product areas. So the Post-market BRB with MedWatch Plus is pretty far along. We're in the throes of implementation of one of the projects. We're following that up with the database analysis in products. The Pre-market Business Review Board is working right now on a common format and use - how would we use a common electronic document room for the FDA. So if we put all the documents in a common EDR, then that obviously makes it easier

for us to go and analyze and everybody to access the documents. In the Quality Business Review Board we've identified the very biggest problem that we have is we need to establish a registry for establishments. Establishments are facilities that make an FDA-regulated product. And we need to have a stable inventory of those where we can identify who makes a product, what products are made there and what is the geographical location of that around the world, not just domestically. And that might seem obvious, but it is not at all easy to achieve. And so that BRB is working on getting that common across the FDA, how do we identify these establishments, what are the data standards, what are the obstacles for doing this and so forth and so on.

The Admin BRB is beginning work in mid-July on administrative processes, and then the Scientific BRB, Scientific Computing is just starting up. So I know that'll be of most interest to you all and you probably feel like why did we wait to start this one up, but frankly we had to get automation and planning for automation for our regulatory processes organized before we

started on the Scientific BRB. NCTR is going to be a hub for a lot of this scientific computing activities and they're going to hold some of the databases I'm going to talk about in just a minute.

So if we go to the next slide, this is again one of these very busy slides, but this just shows on the left, the square box on the left is the Post-market Safety Business Review Board, and it reports up through the Bioinformatics Board and up to our Management Council of the FDA. And under it you see there are all these pieces on policy and IT and finance and enterprise architecture. All these people come together, but it's mainly the business experts who are deciding you know what the plans are for MedWatch Plus. But it's supported by all these people, the policy people, IT and so forth. So that's sort of the structure and you don't have to concern yourself anymore with that, but I'm showing this to show this is a very significant effort. We have to have a lot of project management. We're putting a lot of people and time into this effort and we hope to come out of these with - we'll have road maps for how we'll go from where we are now which

is an agency - have multiple databases and systems scattered all around the agency dedicated to different products to a few common applications that serve the entire FDA. Okay, that's where we're going to go. And what we need is the transition plan. Okay, we want to go here. We want to have one way to submit adverse events to the FDA and we're here now and how do we get from where we are now to where we all want to be. So this is you know across the agency. This will really enable a lot of things that we need to do in the future I think that the subcommittee and the Science Board is probably going to recommend to us. Next one.

Ongoing projects. Now, I'm going to skip to talk about some of the projects - yes, I'm sorry Ken. I'll hurry too. Because what I just showed you is mainly organization which is very necessary, but I think isn't probably that interesting. The ongoing projects in automation are - these are just examples. There are many, but this demonstrates how we're doing this. We're - FURLS is we have an FDA-wide system for registering and listing products and establishments called FURLS and what we've done is

established a common standard in HL7, Health Level 7, which is a standard - external standard-setting body. We've gone to that body, we've established a standard so that then registration and listing can be standardized, how you do it, across FDA. Adverse event reporting for MedWatch Plus, as I said we have a national standard for that under HL7 which NIH is also, they're also participating in this, for the ICSR, the Individual Case Safety Report. For product labels, you all may know that we now have a system where drug labels are submitted electronically to the FDA and I don't have the slide finished, but DailyMed, the DailyMed is a database that the National Library of Medicine holds and that has all the up-to-date drug labels. They're within a day of their approval basically there at the DailyMed site. Is that right, Steven, within a day? Yes. And so instead of these package inserts that may be a year or so out of date circulated around, we have all the information in the DailyMed. The DailyMed now has 3,000 almost drug labels in it, and probably within a very short amount of time we'll have a very comprehensive inventory of all drug labels, and that's free. Anyone can access that

site and get the current drug label. And we are now working with industry to move toward a process, we've had a Part 15 hearing on this, to actually get the drug labels to be all electronic, do away with the package insert and have an electronic system where any pharmacy in the country or whatever can access the current, up-to-date approved drug label instantly. So that is working, but we have to put that ELIPS process and everything agency-wide. That's really the issue, how does that process which is a model, how does it - could it serve the entire FDA. Next one. And Ken sorry, do you want me to just stop, or?

DR. SHINE: Just go. Just the highlights.

DR. WOODCOCK: Yes, okay. We've harmonized - I don't have it on this slide, but we've harmonized as I said medication terminology. The U.S. didn't have a common medication terminology for how if we have an e-health record right, how do you refer to medicines in there? Well, we've worked with the VA, DoD, AHRQ, NCI and FDA worked together, developed a medication terminology, and now we're going - we're trying to go international with that and how do we

internationally harmonize a drug medication terminology so we all know what we're talking about around the world. We have a standard for submitting study reports and everything to FDA, the regulatory product submission or RPS standard, and that standard is for all FDA submissions, okay. So it isn't to one kind of product.

You may be as the Science Board very interested in our JANUS database. The JANUS database is an analytic data warehouse concept where we have standardized data that would be submitted in all the product submissions, like on clinical trials for example that would all be put in a single data warehouse to allow then scientific analysis across submissions. NCI has helped us build that through their caBIG and that is now being piloted. There's another one that's being done, a similar part of this which is called ToxVision which is for all the toxicology data. So we hope to get the toxicology data, whether it's for food, or whatever it's for, electronically and then it would all be put in this data warehouse for scientific purposes. And we've done this for - a digital standard for ECGs and now we have an ECG warehouse that has over

500,000 digital ECGs, annotated digital ECGs in it. And that we're doing with Duke as a research agreement to do scientific analysis on this data warehouse. Next one.

Now, for the poor long-suffering clinical investigators out there with the National Cancer Institute who provided most of the funding we've developed a system called FIREBIRD which is - would be a central repository for investigator information, and their forms and their IRB information for their studies and so forth, and that would all be in one place and they wouldn't have to send all this stuff all the time to the regulators, to NIH, to the IRBs and everything. They could just point them to the information. That is currently also being piloted at FDA and in concert with the NCI. Next one.

We also put out a RFI recently with the - with NIH on what we call clinical data interchange project. We're seeking partners in the outside world who would run the interchange to send clinical data around to all the people who need it, especially the regulatory agencies. And right now we're reviewing the responses on that and we will be seeking probably a public-private

partnership to do this. This type of network NCI would be willing to give the FIREBIRD application to, for example, and then that could be a public utility that would hold that data on the clinical investigators so everyone could use it. Next one.

Genomic data. We've had a workshop on the format of submission of genomic data to the FDA, and again NCTR, CDER, CBER, our whole genomic working group has been involved in that. We've had this voluntary genomic data submission process and we've gotten over 20 - we've gotten maybe over 30 at this point genomic submissions to the FDA and so we're starting to learn about what format those type of data might be submitted to us in. And NCTR has developed some software called ArrayTrac where we can store that and analyze it. And so we're trying to kind of triangulate on how you actually might you know develop a standard for submission of these types of data to the FDA.

Finally - I'm sorry Ken if I took too long - in summary, we're taking enterprise-wide approach to information management at all levels, starting from the business process all the way through how the regulatory submissions would be configured and standardized all the way to the

scientific data, the data warehouses we're building that would actually enable us to do more advanced analysis. The focus right now is on standards development, process analysis and standardization and modular applications. This systems-oriented architecture approach. We're working with HHS, their AHIC on - which they're working on the e-health record and so forth, and with many federal and private partners to get all this work done. So, thank you.

DR. SHINE: Thank you very much, Dr. Woodcock. I do want to have an opportunity for the panel to ask questions. Just from a practical point of view, is there a chief information officer for the agency and who is that?

DR. WOODCOCK: Yes. Tim Stitely has recently come onboard in the last few months as the Chief Information Officer.

DR. SHINE: And what authority does he have in terms of providing guidance for this activity so that it doesn't fragment over time?

DR. WOODCOCK: Well, he's in charge of the IT organization for the FDA and the IT resources and he is part of the Bioinformatics Board and is working - you know, we're working as

a team on this.

DR. SHINE: Obviously there are lots of pieces to this, and there are lots of individual board BRBs as I think you put them, but is there if you will an ultimate template that someone can look at and say this is where we want to be five years from now and that everything needs to fit into that?

DR. WOODCOCK: Yes. The BIB, the Bioinformatics Board, is the ultimate board in charge of that and they're working on developing that. We have a common vision and we know what it is, but it is hard to explain and so we need to work on a communications plan so that we can actually explain this in a reasonable way to everyone.

DR. SHINE: But there is some document that describes that?

DR. WOODCOCK: We have vision of where we're going which is basically you know about getting access to all the data we need and being able to manage all those data and do this all in a paperless manner.

DR. SHINE: But that's going to be translated into an information system and what I'm

interested in is the description of what you want that system ultimately to look like. DR. WOODCOCK: Right.

DR. SHINE: And you've got that - that kind of specific description is available?

DR. WOODCOCK: It isn't available. We're doing that right now because we have to make a map of not only where we want to be, but where all the different pieces are now and how they will converge into these single -

DR. SHINE: As you know, there's lots of experience with this kind of thing in lots of places.

DR. WOODCOCK: Oh yes.

DR. SHINE: To what extent have you used either consultants or other kinds of mechanisms to help you with the process?

DR. WOODCOCK: We have used a specific type of business process mapping tool and the consultants that work on that. And so to put all this - to map all the business processes into software and get agreement and develop the requirements and so forth.

DR. SHINE: Gail Cassell's just joined us, and Gail, everything you wanted to know about

IT at FDA was just reviewed in order to get it on the table before you got here. Susan?

DR. CASSELL: I'm very sorry that I missed it and would add that, as you know Ken, that the examination if you will of the IT infrastructure is a major part of our -

DR. SHINE: Janet made reference to that.

DR. CASSELL: I'm sorry, okay.

DR. SHINE: And she's indicated that it had already been useful in terms of some of those interactions.

DR. WOODCOCK: It's already been very helpful.

DR. SHINE: Please, comments from the board.

DR. SASICH: Janet, thanks a lot, and if I could get to something a little bit more practical instead of broad overall vision. You may have touched on this in the common document room, but boy it would be a help to a whole lot of people if the public could search for approval packages which they can on drugs at FDA, but maybe more importantly briefing documents and Best Pharmaceuticals for Children's Act executive

summaries just by a drug name, and some of this is almost impossible to find. The second thing is will it ever be possible to search DailyMed as a single database? For example, so we could look at all of those labels and actually count how many labels contain FDA-approved patient information that's never distributed.

DR. WOODCOCK: Yes, well that's a very good point and we can take that up with the National Library of Medicine as far as what type of analysis tools or other you know enhancements to the DailyMed. Of course we've been focused on getting that up and running, and believe me that was a huge, heavy lift to get all the pieces together to get that up and we're very thankful to the National Library of Medicine for doing their part on that. But we - that's a very good point and we can talk to them about that.

The other piece, we are - and I didn't bring this up, but we're going to make a major overhaul of our website and we have a webmaster in place who I think is very, very good and they're doing all kinds of testing to see, you know usability for various parties. It might be useful for you to send in some comments about the kind of

things you want to do so that is definitely put on the list. Some of it you know, whatever is public, we're able to make publicly available now we can fix probably. I think one of your issues is we're behind on redaction, it's hard to put a lot of this stuff up because of the burden of redaction and so forth.

DR. SASICH: Actually it's become pretty good lately. It's just - I think it has. You know, it could still be improved, but it's just the -

DR. WOODCOCK: Searchability.

DR. SASICH: Yes. You'd be surprised how many emails I get from all over the world, how do you find this stuff on the FDA's website, even within this country.

DR. WOODCOCK: Yes, well I think that's fair. I feel the same way about it, okay, and we are making a major effort to revamp our website to make it more useable.

DR. SHINE: David.

DR. WOODCOCK: There's a tremendous amount of information on it. The question is how you access that information.

DR. PARKINSON: Just a comment, an

observation on just how important this initiative is. I'm speaking from the perspective of clinical investigation where the opportunities for the FDA to contribute to standardization of how much data and in what format that data is collected will lead to huge gains in efficiency that will benefit everyone, most particularly patients ultimately. One of the experiences, my own interactions with caBIG, and I know you've had lots of interactions as well, is as soon as those standards are put in place, then there are lots of vendors to move in and incorporate those standards into their own software packages and in the case of clinical investigation companies into their own business plans. So the system can be leveraged hugely as I'm sure you're aware by some of these standardization activities. And you know, you might want to comment on activities towards those, but just a huge gain for this area of information collection.

DR. WOODCOCK: As part of our BIMO initiative which I presented to this board in the past about two months ago we had a public meeting with the DIA on data integrity and data standards in clinical trials, and it played off a meeting we

had at the IOM I think in 2001 or 2000 on this same topic. And I think now the energy has come together and the desire that we have to do something about this situation. So CDISC is doing an initiative called CDASH with the FDA and many other partners, the NCI, NIH and so on, on better standards with actual case report form, okay, and standardization there. So we're trying to get down to the investigator level. And at this workshop we went over all the other obstacles there are to maintaining quality in clinical trials, quality of the data, quality of the human subject protection. But I think the energy is there now, and that's what we think, that we may - we can probably do a public-private partnership because this is by no means just the FDA's role, it's mainly the outside to try and move this part of the effort forward. And we'll do that under the BIMO initiative.

DR. SHINE: Thank you, Dr. Woodcock. I would suggest that at some point you might want to get somebody like a Bill Stead at Vanderbilt who pioneered how you bring together multiple databases in an immense organization and rationalize all of the components and just have

them take a look at what you're doing from 3,000 feet. But there are so many forces here to be - centripetal forces pushing in a number of directions. If you can work this so that you in fact have consistency, ability to communicate as you point out with appropriate definitions that would be terrific. And I would just urge you to have someone almost as a project monitor looking at this because even with your board, given the representation it's going to be hard to do that.

DR. WOODCOCK: Yes.

DR. SHINE: But it's an enormously important enterprise and congratulations on moving it in the way that you have.

DR. WOODCOCK: Thank you. And I will - I'll get with you about the names. I know Tim Stitely our CIO is bringing in some consultants to look at this.

DR. SHINE: And he may have the right people. I'm just - I just think it's so important that being able to look at it from time to time, and make sure that you're really on the cutting edge of how you integrate these information systems is important.

DR. WOODCOCK: Great, thank you.

DR. SHINE: Thank you. The next portion of our meeting is devoted to a report to the Science Board with regard to risk assessment in regard to melamine. Those of you who have been following this in the media know that the situation initially developed in which animal feed was found to be associated with deaths of pets. Subsequently it became clear that scraps of material from the feed that was being prepared for animals plus dust and other collected material had been collected by the manufacturers and made available to other manufacturers who produce feed for fish, poultry and hogs. Once that happened there was an immediate need to address the issue with regard to the safety of the food supply for humans. I have been very impressed by the speed with which FDA and USDA both moved aggressively to try to meet the challenge produced by this.

We're joined by - and I apologize Carol, it's Maczka? Carol Maczka who's Assistant Administrator for Food Defense and Emergency Response from USDA who has joined us for this discussion. We're first going to hear from David Acheson who has already been referred to by the commissioner who is Assistant Commissioner for

Food Protection. He is going to give us an overview. Then David Hattan is going to talk about this risk assessment and the conclusions and how rapid peer review was done of those. We'll then have an opportunity for some discussion with the board and an open hearing, and then the board will immediately before lunch bring to closure what it believes ought to be done with this risk assessment, whether there are additional things that ought to happen and what the agency and perhaps the USDA might consider for the future. David, I think we have enough time. This is a very important subject. We'll take whatever time is necessary for the presentation. Why don't you proceed.

DR. ACHESON: Thank you. First of all, I would like to reiterate the commissioner's gratitude to the Science Board and the subcommittee who stepped up to the plate in real short order to help us with this problem. It was a critical need and we really appreciate it. What I'm going to do is to try to paint for you all the big picture of the melamine outbreak so you can see how the specific request for the risk assessment piece fits into the big picture because

it is only a piece of the whole puzzle. And what I want to try to do is to paint this in the context of a timeline because there were certain things tracking in different directions and what I would try and do is to build up a picture for you so you can see how it fits together.

This whole situation began in March when FDA received a call from a pet food manufacturer, actually on March 15, informing us that they had had reports of cats and dogs dying during an experimental feeding process. This pet food manufacturer had reformulated their pet food and as part of a palatability study had been feeding it to dogs and cats in a controlled environment and a number of those animals had succumbed within 48 to 72 hours of having received the food. Clearly that raised a lot of alarms with them. They went back and looked at their records of - in recent months of complaints related to that type of food and they found five or six complaints, again dogs and cats, reports of the animals either getting ill or dying. And the common theme between the reports that had been called into the company and the feeding study was that there was a suggestion that the animals had

died of renal failure. That led, as I say, on March 15 for a call to FDA telling us that the company was going to undertake a recall of this pet food. They didn't know at the time what the problem was.

The next day FDA inspectors went, visited the establishment, collected samples, and then the process began of trying to understand what the problem was. And again, there were a number of avenues that were being pursued. Obviously the first question was is this a new product and the answer was no, it isn't. Then what's changed in it? And the answer to that was that the company had reformulated the product beginning in December 2006 and the change they had made was to use a different supplier of wheat gluten. So obviously Detective Work 101 is going to make you focus in on the change, the only change they had made that potentially resulted in these problems was the wheat gluten so that clearly comes to the top of the list of likely suspects.

The material that was collected at the facility on March 16 was sent to the FDA labs, Forensic Chemistry Center specifically, with a

request to start to look at it to see if they could find something in there that could be responsible for the sickness and the deaths in the pets. During that process there were again two parallel tracks going on because there were a number of labs looking for this suspect compound or compounds. And early on there was a report that the problem was related to aminopterin and there was a lot of press around that. Aminopterin is a compound that is a folic acid-type compound. It's toxic. It's used as an anti-neoplastic agent. It had no reason to be there. To cut a long story short, there was a lot of concern that this was the problem, that's what was causing it. It didn't pan out. We were unable to confirm that. We were unable to confirm that even in some of the samples where the original positives had been found. We got hold of some of those, looked for aminopterin, couldn't find it. So I think - I just want to mention that to put it aside because there was no indication as the science unfolded that this was related to that compound.

So as I say, the hunt was on to find out what may be responsible for this. Well, by March 22 the FDA labs had determined that melamine

was present in the pet food samples. The other thing that they had done was to look at the wheat gluten, because as I said the indications were that the wheat gluten was the common denominator here and was potentially the source of the problem. And initial analysis of that revealed the presence of crystals in the wheat gluten which didn't appear to have any rational reason to be there. This wheat gluten shouldn't have large amounts of crystals in it and there were lots of them. So that raised a question of what were in these crystals. Soon as the melamine was found, the immediate sort of health question - and remember, right now this was totally focused on pets. There was no human element whatsoever. The immediate question was could the melamine have been responsible for causing renal failure in the dogs and the cats. So the analysis began, looking in the literature trying to get scientific input on whether the melamine could do this. And there were a real paucity of studies on melamine, but there were some and the indications were that very high levels of melamine could cause development of bladder stones and subsequently tumors in rats when they were fed very high doses. Now the doses

that the rats were fed appeared to be significantly higher than the doses that we were observing in the pet foods. So there was a disconnect right off the bat. It was if this was melamine causing this, how come it takes so much more melamine to cause the problem in the few animal studies there were. There were no good studies - well, there were no studies in cats, period. And so the veterinarians in the organization began to think about that, and the cat renal system is a little different, and it may be that those animals are especially susceptible.

Well, that brings you back to the crystal issue. These crystals were found and the question was what was in these crystals. An analysis of those crystals revealed that in fact they contained melamine and a number of melamine breakdown products, and that was the point at which these other compounds began to surface, particularly cyanuric acid. Now, melamine itself is - it's a compound that's very high in nitrogen and I'm going to get back to that in a minute. In a mammalian system it is not metabolized per se. It is not metabolized in the human body that we know of or in cats or dogs. When melamine is

exposed to bacterial breakdown it will break down to other compounds, including cyanuric acid, a compound called ammeline and another compound called ammelide, and there are several others in that breakdown chain as it breaks down from melamine. So there was a plausible explanation as to why cyanuric acid and ammeline and ammelide may be present, simply because they are breakdown products. And they may even have been part of initial impurities as the melamine was being manufactured. So it then appeared that this wheat gluten and the pet food didn't just contain melamine, but it contained melamine and cyanuric acid and some of these other compounds. As the story unfolded, it was then speculated that in fact it was the combination perhaps of the cyanuric acid and the melamine particularly that when in the renal tubular system was able to precipitate, form crystals and lead to renal failure.

Let me continue - that's going off into the potential pathogenesis of the problem. Let me come back to the timeline. Once we had realized very clearly that it was the pet food, it was likely the wheat gluten the question was where did

the wheat gluten come from. This is the trace-back process. We had the call from the company. The company said the wheat gluten was likely the problem. We could confirm that. The question was where did the wheat gluten come from. That took us back to a company called ChemNutra. So the question was to ChemNutra where did you get your wheat gluten from and where else did you send it. So you're continuing trace-back, but you're also asking questions to trace forward where else did it go. That process as you know unfolded and obviously I'm sure you're all very well aware that ChemNutra received their wheat gluten from China. As that unfolded, that part of it, it was clear that ChemNutra had been receiving this type of wheat gluten for awhile from China and had been sending it to this particular pet food company, and that then led to a host of recalls. Rather than the original product that was taste-tested, the recall system expanded as we learnt where this ChemNutra wheat gluten had gone and that was why this ball kept on rolling and expanding. It was like a snowball going down a hill as the number of recalls were getting greater and greater and greater, as this trace-forward web was expanded.

About April 20, we got notification from another company, completely separate company - actually no, I'm sorry, it was probably about April 16. Get my dates right here, April 16. We had a call from another company and part of what we had been doing in that March timeframe is getting the word out that there were problems with the wheat gluten and several companies were starting to do their own testing and looking for the presence of melamine in some of their ingredients. Another company on the West Coast used rice protein concentrate as an ingredient for pet food. They got that rice protein concentrate from China. They looked in it. They found melamine. They informed us of that. That rice protein concentrate had also been used to manufacture pet food. Further analysis showed that that rice protein concentrate also had cyanuric acid, ammeline and ammelide, so there were a lot of parallels there, and they were associated with some reports of illness in animals. Turned out that rice protein concentrate had also come from China and different company from the first one, unrelated to the wheat gluten story. So there were two parallel tracks going

on.

The next chapter of this is the point at which USDA became involved because up to that point we had been dealing with the wheat gluten and the rice protein concentrate going into pet foods. Part of the trace-forward process had been to ask the question did any of this go into the human food supply. That was obviously an initial and key concern to us, and the answer was and still remains that no, it hadn't. Even though obviously wheat gluten and rice protein concentrates are common ingredients in human food, they hadn't gone into the human food chain directly. However, what we then learned from the rice protein concentrate situation is that some of the scraps from the pet food manufacturing process that they use - and when I say scraps, what I'm talking about is essentially the material that's end-of-line, materials that's left over after they finish bagging, things that are okay, salvageable, but they just haven't wound up in the packs going to the pet food, the company collects this and they shipped it to a local hog farmer. This is the point at which the story then branches into the human food supply because what we then learned

was, the good news was that this was a local hog farmer who didn't sell hogs to vast quantities of people. It was a small operation, but this hog farmer did have hogs that he kept for slaughter for human consumption. That was the point at which USDA became involved and we worked with them to then ask the question - we've got it in hogs. Number one, what's the risk to the hogs and number two, what's the risk to humans if they consume the pork from those hogs. That was the beginning of the question that essentially are framed in the risk assessment itself. And I am not going to go into details of the risk assessment. My colleague David Hattan is going to speak to that in a minute.

So that was going down the hog road. Clearly that raised the question with the original recall that I told you about with the wheat gluten, well where else did that go. Did that go into pet food - into human food via animals? And the answer to that question was yes. And at the end of the day with those two tracks, what we found was that scraps from the original wheat gluten problem and the rice protein concentrate problem had gone into both hogs and chickens. So

we now were faced with a question of the danger to humans from consuming the chickens or the hogs. And one of the important differences there was first of all there was no evidence that either the chickens or the hogs were sick - and we looked into that - unlike the cats and dogs. The second was that the chickens and the hogs were not fed pure pet food. It was cut to some extent with other products. Unlike the cats and dogs where the pet food was the exclusive diet, the hogs and the chickens had other components in the diet. So in other words there was a dilution effect.

The next piece to this puzzle came in when again through trace-forward and working with our international colleagues we learned that ChemNutra had essentially shipped a batch of this potentially contaminated wheat gluten to a company in Canada. That company in Canada had used the potentially contaminated wheat gluten to manufacture fish feed. That fish feed had then been imported back into the United States to feed fish in the United States. And you thought the BiB was complicated. That fish feed had come into the United States and had potentially gone to 198 fish farms. So we got out there, tried to get

that information, well what are these fish farms. Turned out this is a - we had a little bit of good luck here. Only two of them were commercial operations where the feed was going directly into fish that were being currently harvested for human consumption. All of the rest of them were basically hatcheries where the feed was being fed to tiny little fish that had got months and months to go before they would be ready to be consumed, and those hatcheries typically grow fish that are going to be released into lakes and rivers, or for breed stock, or for sports fishing. They weren't going directly into commerce.

We learnt that there were two commercial operations that were dealing with fish that had been fed this contaminated feed. And I want to again emphasize that this feed had the same components, it had melamine, cyanuric acid, et cetera, in it. We were able to test by that time - let me back up a little bit because there was another parallel track. Again, early on not only did we not know much about the toxicity of melamine, we didn't have an assay to measure it. The FDA Forensic Chemistry Center came through very quickly with an assay to measure initially

melamine and then these other compounds. And one of the things that we did with that was to post that method on the web and essentially broadcast it to the world that it was up there and anybody who wanted to check an ingredient for melamine or melamine-related compounds could go ahead and do so. And that was actually how the rice protein concentrate surfaced, because of that outreach and that publicity. So I think that's a lesson learned for us which is a good one.

So we were able to measure these compounds in the raw ingredient. We weren't able to measure it in the flesh of either the chickens, the hogs, or the fish initially. And that was obviously a key question because you knew the concentration in the pet food, you knew the dilution factors, but obviously a key question is well what's residual left in the flesh of the chickens, or the hogs, or the fish at the point at which they may be consumed. So again the labs worked at developing assays for melamine in those various other matrices. By the time the fish feed piece had worked through and we were going to these two commercial companies to look for the presence of melamine, we were able to test the

fish and in fact found that they were negative. So that was essentially good news. And the companies put the fish on hold for a period. Once we knew it was negative they were released.

Various other things were happening around this, just to sort of continue to paint the picture. As I told you, the wheat gluten and the rice protein concentrate were both from China. We had put import alerts on those two companies which basically meant that they could not import product into the United States without showing to us that it was safe and the onus was on them to do it. During the course of this in the international outreach we learned that similar problems had occurred in South Africa with corn gluten and what that immediately did to us was raise the question this could be all over the place and we've got two, we now had a third. We didn't have that one in the United States, and so what we did at that point was to put out a countrywide import alert on Chinese vegetable protein concentrates. All the indications were these problems were from China. The South African shipments indicated it was China too. So the reaction that we did was essentially if you want to import a vegetable protein

concentrate from China, you had to prove to us that it was safe to do so.

Another parallel thing that we did was to develop something called the Protein Surveillance Assignment. And this was a mechanism that we put in place that was based on some of the food defense things that we've done that when we see a problem, what we are going to do is to initiate an assignment to go out and test in places where we haven't currently found there to be an issue. We knew the two pet food manufacturers, we knew the fish. What we didn't know was any other protein concentrates from China that had come into the U.S., not part of these two companies, potentially problematic. We had no idea. Clearly there was the potential. We had two companies that had imported. So we initiated this assignment to go out to manufacturers that we knew of and could identify who used protein concentrates from China to do two things, number one, raise their awareness about this, suggest that they test if they're not. We took samples and tested as well and that assignment began several weeks ago during the middle of this and is continuing to run forward. And we've covered a

lot of ground with that and so far have just raised awareness, but haven't found any other problems.

The final chapter of this was again through awareness. There was then a company who was testing product. They used a feed that they were - they just questioned about. They had two sources of their feed. One was from a United States company and one was from an overseas company. It was not China. They were suspicious frankly about the overseas company. For no good reason they just thought well we better check it. And so they checked both their ingredients from the overseas company and from their American supplier. At the overseas company it was fine. The American supplier had melamine in it. This is the final chapter of this. This was product that was manufactured as a feed in the United States. Melamine was added to the product in the United States. Interestingly the levels of melamine in this final one was significantly lower. The cyanuric acid was there, but almost nonexistent, so there was very little cyanuric acid in there. This final chapter part, that product had been used to produce feed for cattle as well as fish

feed. The cattle feed was largely for domestic purposes. The fish feed was largely for export. The good news there was that the levels in this feed as I said were significantly lower than the first two things that I talked about.

Obviously one of the questions that you may have is well why was melamine put there in the first place. Let me just address that up front. As I said, melamine is a compound that contains - it's a very high level of nitrogen. It's used as a fertilizer in some countries. It's not approved for that in the United States. One of the ways that companies typically check the protein content of an ingredient is to measure the nitrogen content. So wheat gluten is obviously an ingredient that's meant to be high in protein. The companies or industry will typically just measure total nitrogen as a marker of total protein. The manufacturers of the wheat gluten and the rice protein concentrate had obviously figured out that they could artificially raise the nitrogen content and thereby the apparent protein content by simply adding melamine, a very high nitrogen-containing compound, to it and you essentially fool the analysis. We don't believe

that it was done with any deliberate reason to cause harm to either pets or humans in the United States. We believe it was most likely done simply to raise the apparent nitrogen content.

With regard to the American-based contamination, as I said the levels were lower. One of the things about melamine is it's a good binder and if you think back, certainly when I was a kid the melamine plasticware that we used to eat off, it's the same stuff. You polymerize it and you can turn it into a plate or a cup or a spoon or whatever you want. It's still around. So it's actually a good binding agent and it would appear that it was being used actually in this feed as a binding agent to make pellets stick better, simply because of its scientific properties. Nothing to do with impacting the nitrogen content of the final feed.

Just to throw one more wrench into this so that - for the sake of completion, our labs looked back at the rice protein concentrate and the wheat gluten which I've told you contained melamine, cyanuric acid and these other compounds. And when they began to look at that in more detail for other things, because obviously the

question was is there anything else in there. And I'm not about to spring some other chemical on you, but what it turned out was that most likely this was not wheat gluten at all. What it was was most likely largely wheat flour with a little bit of wheat gluten in it. Wheat gluten is obviously a component of wheat flour so it appeared to be wheat flour with some wheat gluten and melamine, the end result being that when you test it for nitrogen it looks like it's pretty high-quality wheat gluten, but in fact had high levels of wheat flour in it. The rice protein concentrate turned out to be exactly the same stuff. It was wheat flour, wheat gluten and melamine. It wasn't rice protein concentrate specifically. It wasn't clear whether there was any rice protein concentrate in there, but it certainly was - so not only was it melamine-containing, but it was also mislabeled as well.

I've given you a very broad overview of the whole story. The risk assessment was really driven out of the need to understand the human health risk with regard to the chickens, the hogs and the fish, and so with that I suggest that we now focus on that specifically with what I've said

as background, and if we need clarification I'll be happy to take questions later.

DR. SHINE: Let's do that. Let's hear about the risk assessment and then we can ask questions of both of you. David Hattan.

DR. HATTAN: Thank you, Mr. Chairman. Can everybody hear okay? First of all, I'd like to thank the board for the invitation of reviewing our risk assessment with melamine and its analogues. My name is David Hattan. I work as a Senior Toxicologist in the FDA Center for Food Safety and Applied Nutrition in the Office of Food Additive Safety. I would also like to point out that accompanying me today are a number of FDA staff and also USDA staff. As far as I know we have Dr. Robert Buchanan from our center and Dr. Susan Carberry and we may have a representative from Center of Veterinary Medicine. I'm not sure though, I don't have her name, and perhaps also from ORA. The Food Safety Inspection Service of the USDA has Dr. Carol Maczka and Dr. Michelle Catlin.

Well, you've heard the fascinating part of this story from Dr. Acheson. Now you'll hear the portion that perhaps is - I think it's very

important, but I don't think it's as exciting as the part that you just heard. We're going to be talking about a safety risk assessment for melamine and its analogues. This particular - could I have the next slide, please? This particular analysis I'd like to emphasize from the outset the purpose was to evaluate the risk to humans from consumption of pork, chicken, eggs and fish that had been inadvertently fed animal feed containing melamine and its analogues. And so you will find that this risk assessment is restricted to this particular limited purpose. And in the - throughout this talk we'll be discussing the safety and risk assessment model used, the evaluation of toxicity information, especially determination of a no-observed-adverse-effect level, the application of uncertainty factors or safety factors, development of intake or exposure scenarios, a determination of margins of safety, a calculation of levels of concern, and near the end we'll be discussing the peer review report and finally some ideas for future research recommendations. Again, I want to emphasize that in our view this was a short-term occurrence, this contamination or adulteration episode, and not a

long-term occurrence, and that drove much of the risk assessment that we did.

Now, I'd like to discuss some of the toxicity data that we utilized. From the literature there's an acute LD50 in rats of about 3,200 mg per kg body weight per day, and in the universe of chemicals that's a substance with relatively low toxicity. There's also a 13-week feeding study in rats and the no-observed-adverse-effect level was 63 mg per kg body weight per day and that is the particular study that we used as the basis for calculating some of our other values in this risk assessment. The reason that we used this study is that we felt that it was of long enough duration to give us an idea of what multiple exposures to the melamine compounds, what the effects would be, but it wouldn't be so - it would also have some of the parameters examined that we felt were useful to evaluate this in a relatively acute exposure scenario. You will note in the next bullet that there is also information from a 2-year bioassay in rats, and interestingly the no-observed-adverse-effect level is somewhat higher, 263 mg per kg body weight per day. But of course in a bioassay they look at different things

than they do in a short-term feeding study. Also, just to give you some indication of the variation, the susceptibility of various species to this material, there's also a 13-week study, a feeding study in mice and you'll see that the no-observed-adverse-effect level in it is surprisingly high at 1,600 mg per kg body weight per day.

If you look at animals from one of these studies, this is what you will observe. There's reduced food consumption, reduced body weight, that eventually there is crystalluria that occurs, crystals start precipitating out in the urine, and if exposure continues long enough and the doses are high enough you get actual bladder stones forming. The bladder stones within the bladder result in an overgrowth of the inner lining of the urinary bladder, a hyperplasia of epithelium, and later on as Dr. Acheson indicated chronically that can lead to bladder tumors. Interestingly enough however, this information is on melamine itself, quote unquote, that single compound, and there was no evidence of renal failure or symptoms of renal failure in these studies. This may suggest something about this combination of products, and we'll talk about that

a little bit later. The dose to elicit toxicity as is indicated so far varies widely with the species, but once you reach that toxic threshold the symptoms are more or less similar. There is a little bit of information that we have on histopathology of cats who died from eating the contaminated pet food, and indeed they did show abundant renal crystals. And when there was a subsequent analysis of those crystals it was confirmed that there was the presence of melamine and cyanuric acid.

Just to spend a bit more time with that chronic study, it was a National Toxicology Program lifetime study. We've already talked about what the no-observed-adverse-effect level was. In the male rats in that study there was an increased stone formation in the bladder and an excess of bladder tumors was observed. There's a very close association between the occurrence of the stones and the occurrence of the tumors, so it almost appears that the stones are prerequisite for the tumor formation. Let's skip down to the bottom bullet then. It is interesting that - and this is also sort of an indication of the relatively non-toxic nature of this material to

the cells themselves that there are no other tissues that showed excess tumor formation. Also, we assumed that all of these melamine compounds are equipotent and that may or may not be correct. Only further time and experimentation would confirm that, but for the purposes of this risk assessment that's what we assumed. We do have information on cyanuric acid and on melamine, and with respect to those two compounds they're well-absorbed from the GI tract, they're distributed through the total body water and they're rapidly excreted in the urine with a half-life of about two to three hours.

Now, what I have to do is speak just for a few minutes on some intake scenarios. Okay, we have the picture with respect to the toxicity of this material. Now we're going to talk about what the intake levels might be under various proposed scenarios. Some of the assumptions for the development of these intake scenarios for the melamine compound is that they were all treated as a group and not a single compound. We assumed that the tissues were contaminate with 100 parts per billion and that was broken up into melamine at 50 parts per billion and the other three

moieties, cyanuric acid, ammeline and ammelide combined at a level of 50 parts per billion. The FDA and FSIS data from the tissue levels from hogs fed the contaminated ration informed some of these assumptions. Now, that 100 part per billion is a conservative estimate of the limit of detection of the assay, but it was chosen to assure - ensure a conservative estimate of exposures. And another assumption was that all the pork, poultry, fish and egg products were from animals fed contaminated feed until just prior to slaughter.

Now what I'd like to do is spend just a couple of minutes on the intake scenarios themselves, the actual numerical values you'll find in the risk assessment that you have copies of. Because of the restrictive time, I just wanted to deal more with how we did the risk assessment analysis. The intakes were calculated from the continuing survey of food intakes for individuals. The database used was from 1994, `96 and `98, and the reason those three surveys were used is that they provide a better estimate of exposure. It's a 2-day estimate rather than a 1-day estimate that was changed to later on. This particular survey system is supported by a

sophisticated methodology using commodity codes for the food ingredients and even product recipes so that it does a pretty good job in trying to relatively accurately define what intakes might be under various scenarios. Then what we did was propose three different scenarios. Scenario 1 was direct intake of catfish, chicken, pork or eggs. Intake 2 was the intake of chicken or pork meat and added in the byproducts from - added to other kinds of food products. And then finally Scenario Number 3 is a worst case scenario. And I emphasize that this is an exaggerated case and this is something that you just wouldn't find, but I just wanted to give you some feel for if you went to the outer edge and assumed that the melamine compounds were in all solid foods at the level of 100 parts per billion that would result in 150 mcg per person per day, assuming a 60 kg person.

Now, what I want to do is talk about some of the other derived parameters that were calculated. First of all, a bit of information that we need is a TDI, is a Tolerable Daily Intake, and it's an estimate of the amount of substance that could be taken in daily over a

lifetime without subjecting the person to appreciable risk. Another term of art in toxicology is a point of departure, and in this particular case our point of departure is the point of no animal toxicity from that sub-chronic rat study which the no-observed-adverse-effect level was 63 mg per kg body weight per day. Then note what we do is take that NOAEL and divide it by 100. That's a safety factor or uncertainty factor. In this particular case uncertainty factor is probably a better way of referring to this because there are questions about how the human system would handle this particular material compared to animal systems. And so what we did was we used a hundredfold safety factor, tenfold for interspecies variation and tenfold for intraspecies variation. The resulting tolerable daily intake turned out to be less than 1 mg per kg body weight per day, and note, if you're not familiar with risk assessment processes that this ends up with a value of course, this TDI that's a hundredfold less than the no-observed-adverse-effect level from the animal studies. So the animal studies have a no observed effect, and then you put a hundredfold safety factor on top of

that.

Now, one way you can look at this kind of information to see how much exposure distance you have between the tolerable daily intake and how much the person would be exposed to from eating the levels at these materials as indicated by that survey of eaters. And what you do to determine the margin of safety is simply divide the tolerable daily intake by the exposure estimate for these various products from that survey. And you'll see the margin of safety for catfish is a bit less than 2,000, for chicken it's around 3,000, for eggs and pork around 4,000, and then from combined products about 2,600. Now, you may wonder, well, what's the margin of safety for that worst case scenario where you have very high exaggerated levels of exposure assumed. And in that particular case you still have over a 250-fold safety margin there. So it is 250-fold less than the tolerable daily intake.

Now, some of you may take issue with this next approach, but it's sort of a way just to illustrate how impossible it would be to eat enough food to reach a toxic dose. Just to reach the tolerable daily intake from the food

contaminated 100 parts per billion you'd need to consume, and we assumed that people take in a kilogram and a half per day, you'd have to, when you go through all of the equation there, you'd have to eat 831 pounds of food in order to get the tolerable daily intake. So I think you can see the safety margin involved there. Another way of looking at this is to develop a level of concern, and all we do to do that is take the tolerable daily intake, multiply that times the weight of the individual. That gives you the total amount of material you would have to take in to get the tolerable daily intake. Then you choose a level of exposure that you think is appropriate, and we thought a conservative assumption would be good so we used the 90^{th} percentile. What this calculation tells us, that at the 90^{th} percentile level of food consumption what level of melamine contamination you can eat with no appreciable risk. And for these particular products, for pork, poultry, eggs and catfish it runs from around 200 to 450 mcg per gram, or mg per kg of food. So, based on all of the foregoing analysis our conclusion is that on the currently available data and information the results of the safety and risk assessment indicate

that the consumption of pork, chicken, domestic fish and eggs from animals inadvertently fed animal feed contaminated with melamine and its analogues is very unlikely to pose a human health risk.

Now I want to take just a few minutes to talk about the peer review. Again, I would like to join the others and thank the peer reviewers for their very expeditious turnaround of their opinions of our risk assessment. It was greatly appreciated. They were submitted, the risk assessment itself in a written charge and their overall summary of the risk assessment was they felt that the conclusions from the risk assessment were appropriate. In addition, they felt that recognizing the time sensitive nature of the need for these results, that the peer reviewers concurred that the methodology, the data, the assumptions and exposure scenarios used were appropriate.

Now, they did provide us some feedback of some additional things that we might want to think about. For example, they suggested that we might want to consider data from studies of similar compounds, for example the triazine

pesticides. All of these substances, the melamine compounds and all of those other congeners are from the triazine chemical classification. Evaluate the possible chronic toxicity from longer duration exposure. We do have some information on some of these compounds from previous experimentation, but there is a question about what you would see if they were exposed to combinations of these materials. Also, provide more information on the design of the specimen sampling and the toxicology studies.

Now, to spend just a couple of minutes on some research recommendations for the future. It has been suggested by various parties that we determine the concentration at which the melamine compounds crystallize in the urine of different species. That of course could be very useful information. It might help to explain how some species are more susceptible to this effect than others are. Consider possible formulation - actually formation of other, more toxic compounds that might occur during the preparation of the final product. There's heating in that process. And study whether co-exposures to these multiple melamine-type compounds elicit additive or

synergistic effects. It would also be important to improve the analytical methods, especially in the detection of low levels of these compounds in tissues of food-producing animals. And to characterize renal crystals. And I think this is the final slide. Conduct basic toxicological studies in multiple species, get a better feel for the relative sensitivities in various species. Develop early biomarkers for the onset of renal failure. If that could be done that would be quite useful. Study effects, other environmental effects that could be useful or host-related effects. For example, how does dehydration, the administration of common medications like diuretics and other effects and agents on renal excretion of these melamine-type compounds. And then finally, to conduct longer term toxicology studies to assess potential carcinogenic, reproductive and developmental effects. Thank you very much.

DR. SHINE: Thank you very, very much Dr. Hattan. We're now going to open this for questions from the panel and start with Dr. Cassell.

DR. CASSELL: Well, first of all I'm

very impressed with what you've been able to do in a relatively short time and there are a couple of questions that come to mind. One is with as much strain or species variability as there appears to be, it seems to me that one additional recommendation for potential research would be in addition to doing the basic toxicological studies in multiple species it might be wise to look at different strains within the same species, especially of course in rats and mice. I'd like to know whether or not, you know what you think about that, but when I see that much variability within the species it makes me wonder about you know the difference in sensitivity within a species.

And then I guess the other question that I have, it's obvious to me based on all of the work that's been done, this must have required a lot of resources on your part. So when you have an unexpected, unanticipated emergency like this, where do resources come from? What suffers as a consequence of the need to immediately focus and pull people off other important projects, particularly because it's been so I guess crosscutting? So if you could maybe share your

thoughts about that I would appreciate it, and maybe also Dr. Acheson could comment on that.

DR. HATTAN: I think that as far as resources go on the scientific or technical side we were able to take advantage of people who had appropriate training or background within our center and throughout the FDA. And people were unstintingly willing to provide their expertise and time to help us do this. I think everybody realized that this could be a very important kind of adulteration event and especially if it extended to human food in a serious way. But just to answer one of your questions about where do the people come from, they obviously are drawn from other things that they're doing as ongoing activities. What you hope is that you don't get too many of these special things occurring serially and temporally you know adjacent in time because you're right. When they're taken from something else they're not working there.

As far as looking at strains of species, that might inform this process, but I think that there's something sort of unique about these compounds. As indicated by the toxicity information, there's not a lot of direct cellular

toxicity of these materials. In addition to that there appears to be very little metabolism that occurs within the organism itself. Those are the kinds of things that really would contribute to changes based on strains within a species. So you might find something, but at this point in time I don't see you know a big strong reason to do that. Yes, to look at the differential responses in species, I think that's important.

DR. SHINE: Dr. Acheson, do you want to comment?

DR. ACHESON: Sure, thank you. I won't speak to the second part, but the first part I think on resources, I think that's a key question and as you know, our priority is if there's acute emergency, it's public health, public health, public health and we've pulled folk off other things, ongoing prevention thinking, other strategies to deal with it. And I want to also emphasize that this was not solely an FDA effort. There was massive input from USDA, EPA, CDC and DHS in the generation of this risk assessment. So multiple federal agencies got together really fast to do this. And you know the inevitable consequence is that other things will slow down.

They won't fall off the table, but they will slow down as we have to deal with these public health emergencies, but that's the priority and it will stay that way.

DR. SHINE: Dr. Cassell, I just want to take this opportunity to remind you as you go through your science review that when we talk about a science-based or science-led agency we've struggled in the scientific panel with how much of the science needs to be done by the NIH or a variety of other places. This is a good example if you don't have certain scientific capability in-house you're going to have difficulty in responding, and I think that has to be part of our calculation.

DR. CASSELL: I agree and actually I had a follow-on question that bears on that if you don't mind if I could just ask it. And that is there are some I think very important studies that have been recommended that be done, and the real question is kind of knowing what resource constraints are, where will those resources come from. And I hate to keep pushing on that, but I mean I think it really is important because - anyway, I'd like to know where you intend to get

the resources and help out the personnel in order to get these studies done in a timely fashion. And then I guess I just - maybe at break we could talk a little more about why you see so much variation in species, but you wouldn't really expect to see that much within a species.

DR. ACHESON: Let me - there is a really good answer to your question as I'm sure you recognize. What - and this sort of links back I think to Dr. Shine's comment. One of the reasons it's worked so well is because we had folk like Dr. Hattan on staff, toxicologically trained, years of experience, understand the science, the tox and the regulatory process. You've got to have people right there at the end of a phone 24/7 who can do that, and if that gets eroded we're in all kinds of trouble. So that's key, but also there's the opportunity to leverage and I think that this gets a little bit at some of the discussion that was actually happening earlier in the meeting of how can we use the expertise of the Science Board and your connectivity to the academic intellectual world that when melamine comes up we can call somebody, who do you know who knows about melamine, connect us, and then when

the subcommittee comes together we can already have those experts lined up. I mean that's something that we're thinking about and the commissioner has tasked me to think about that in the context of a mechanism in relation to food and feed.

In terms of the resources to do this, you know we faced the same question after spinach. There's a lot of well, we need to understand how do you prevent E. coli getting on spinach. That requires basic research, dadada. Second thing that pops up is well how do you control salmonella in a peanut butter plant. Well, you need to understand microbial ecology. Every time we get one of these outbreaks there's two slides' worth of $10 million worth of research that pops out of it. And the practical reality is that the FDA cannot possibly do that. We couldn't do all that with the current resources so we have to prioritize. And the priority is going to be based on essentially where the greatest public health risk is lying and with what we have that has to be the way we look at it.

DR. CASSELL: So out of the three things that you've named, the spinach, the peanut

butter and these studies that we've heard this morning, which do you rank as the highest priority of the three?

DR. ACHESON: Leafy greens.

DR. SHINE: Thank you. You'll have those subsequent discussions at the public meeting, Gail. You won't be talking about all those things at lunch. Susan? Susan Harlander.

DR. HARLANDER: I guess my question relates to what other kinds of compounds might be added to these products to increase nitrogen that might have similar effects? And will your research surface any of those other kinds of compounds that - I mean it's kind of a frightening scenario when you think about it.

DR. HATTAN: Do you have a copy of your risk assessment with you? If you do, go to Appendix 1 and for the purposes of economic fraud, or economic leverage depending on how you want to describe it, Appendix 1 shows the structure of these compounds and melamine is the one they get the biggest bang for their buck because there are six nitrogen molecules there. Cyanuric acid they get the least bang for their buck because there are only three nitrogens there and the other two,

ammeline and ammelide are in between.

DR. SHINE: Other questions? Yes please, Lonnie. Go ahead.

DR. PARKINSON: Well, my question - would uric acid be one? Yes. You see, this just looks - as a cancer clinician, this just looks like the clinical setting of hyperuricemia. We have tumor lysis syndrome, we have a lot of tumor cells dying at the same time, you have patients who go into acute renal failure related to mass precipitation throughout the tubular system of the poorly soluble uric acid. There's examples of different types of dogs handling uric acid in different ways. They either do have or do not have the same problem as humans do. This to me - you've made a compelling argument through these very detailed and very complete and laudable studies that this is not a toxic compound in the traditional sense. This looks to me like a physical chemical property issue related to renal excretion and acute renal failure related to differential species handling of that, probably coupled with a concentration intake issue. Does that make sense?

DR. HATTAN: Yes, it certainly does.

DR. SHINE: And in that regard one of the questions I had was if you did have hyperuricemia in a patient or in an eater, someone, what does that do to the overall solubility?

DR. HATTAN: I think you would just enhance the probability that the individual would have precipitation.

DR. SHINE: So the question is to what extent in individuals who are hyperuricemic would the toxic - the levels that would be of concern vary?

DR. HATTAN: I think that we would have to do some studies to really get an accurate characterization of that, but thankfully at the levels of exposure that we have here I don't think anybody is at risk.

DR. SHINE: That would be my guess as well, but I was thinking about interactions. Lonnie King was - those of you who have seen the report know that the comments by the peer reviewers are anonymous. They're identified as Reviewer 1, 2, 3, but they are identified in a list. Lonnie was one of them. Would you want to comment as well as have any questions, Lonnie?

DR. KING: Sure. Thanks very much and Dr. Hattan thank you. I think this is a job well done and I agree with the conclusions. Also, the research recommendations, especially the one about longer term studies to look at potential chronicity effect.

I have kind of three questions that maybe you would address. One has to do, could you briefly discuss, or Dr. Acheson, about potential background that we have to melamine through plastics, and does the margin of safety consider people that actually eat pet food directly which is not a great topic before lunch, but it does - it actually does occur, it's clearly relevant. The second would be the idea of triazine and looking at that compound. A lot more studies and data available, and is that something that probably should be considered more in terms of maybe even a different pathway? And then the final question would be one in terms of are there issues with these compounds combining with resins after cooking and perhaps forming other compounds that are even more toxic that need to be looked at. Thank you.

DR. HATTAN: You may have to

recapitulate your questions, but -

DR. KING: Background exposure.

DR. HATTAN: Yes. There is background exposure, but in most cases it's of an occupational nature rather than a general environmental exposure. It's found, as Dr. Acheson has indicated already, it's very useful as a starting material for the development of polymers, plastics. It's also used as an adjuvant in the development of fertilizer, amino-type compounds complex with the triazine part of it, of melamine very nicely. And it's also used interestingly enough, this combination of substances, four substances, is used in some polymers as a flame retardant. So those are the kinds of exposures that we're aware of at this point in time.

DR. KING: And then about the potential combination with resins or after cooking, could you actually create a more toxic material?

DR. HATTAN: Again, anything that I would say at this point would be speculative. I don't think you can eliminate that possibility, but I wonder if - I think it could go both ways. You could have the breakdown of the molecule maybe

to something more toxic, but if it combined with other materials it might become less toxic. So I think - the only way you could really check that is to do the research and see.

DR. KING: Last point, just the idea that also CDC put in effect kind of a surveillance system to look at early warning, so was there an increased incidence in renal failure in cases in emergency rooms or in hospitals, and we didn't see that at all. It just gives you some added comfort as you look at kind of the risk analysis.

DR. ACHESON: One point that you did raise is about people eating pet food, humans eating pet food. I think that is a potential concern. Two thoughts on that, and you know it's a speculative answer is that it's unlikely that the pet food would be the exclusive diet. It's possible, but I mean that reduces the likelihood even further and I don't think we particularly know whether the cat and the dog renal system was more susceptible than the human which I think is potentially a factor. You know, the hogs and the chickens, thousands of them got fed this stuff at various levels, but not exclusively. They were physically fine. So I think, I don't know - and

as you point out, you know we did put that surveillance in place with the Centers for Disease Control to see if anything popped up and it hasn't.

DR. SHINE: Let me interrupt for a moment. We're running late in the program, but we had scheduled public comments for 10:45. Could I see by a show of hands who in the audience would like to make a public comment? I want to just get an idea of what - we have one. Anyone else wish to make comment? Can we continue the discussion for about 10 minutes and then hear from you, sir? Is your schedule okay? Okay. I just see one hand for the moment, so Janet.

DR. WOODCOCK: I just want to make a comment. Under the Critical Path initiative we expect to receive a set of animal biomarkers for renal toxicity submitted to us next month that have been validated in animals. And they are you know, by design much more sensitive than the usual clinical measures.

DR. SHINE: Other questions from the group? Yes, sir.

DR. SASICH: Thank you very much for the presentation. I guess from the presentation

we don't actually know at this point in time what killed the pets, is that correct?

DR. SHINE: Yes. Kidney failure. Renal failure from stones.

DR. SASICH: But I mean what in terms of the compound. Or what combination of compounds, if it was a tumor, whether these melamine compounds. We don't?

DR. ACHESON: The indications are that the animals died from renal failure.

DR. SASICH: Okay.

DR. ACHESON: Secondary to crystallization and tubular obstruction I think probably. That's - David, I don't know whether you -

DR. SASICH: Okay. And so do - reports have dropped from pet owners to the agency or to companies since the recall?

DR. ACHESON: In terms of numbers of?

DR. SASICH: Adverse events.

DR. ACHESON: Yes.

DR. SASICH: And do pet food manufacturers, do they have a mandatory reporting requirement to the Food and Drug Administration?

DR. ACHESON: No. Not as far as I'm

aware they do not.

DR. SASICH: So that might be an area that's worth exploring. Just a brief comment that was mentioned earlier about siloing of programs and in science. It seems like the issue is much broader than just this pet food incident. I think probably everybody's aware of the diethylene glycol concern in Chinese toothpaste contaminated glycerine coming into the country. I mean we think about diethylene glycol and we go back to 1938 and the elixir of sulfanilamide. And just recently a pharmacy in New York was allegedly importing human growth hormone from China, a compounding pharmacy that wasn't FDA-regulated or inspected. So it seems like it's not just a food or a pet issue, but in our present environment that the possibility for contaminated products affecting Americans could be from a number of different sources.

DR. SHINE: An area of considerable concern to this group. Just clarify. Since recall of these pet foods, have there been any further reports of any deaths in animals from renal failure?

DR. ACHESON: I don't want to say zero

because I'm not tracking those on a daily basis, but I know they've fallen off significantly. There have been some recent press reports of product that was still on the shelf or people had at home, they hadn't heard about that had made animals sick so I don't want to say it's zero.

DR. SHINE: If somebody - if a pet dies of renal failure, is there some mechanism by which one could rapidly determine whether in fact it's associated with crystals in their kidneys?

DR. ACHESON: I think if you did an autopsy on the animal.

DR. SHINE: No, I know technically. What I'm asking is whether - do we have any surveillance mechanism such that we could be certain that an autopsy were done for that purpose?

DR. ACHESON: Oh, no. No, I mean the equivalent of a surveillance for pet illness if that's your line of thinking.

DR. SHINE: Well, I'm thinking of specifically for this problem in terms of -

DR. ACHESON: No.

DR. SHINE: - knowing whether, if something - if there are some reports over the

next month of you know, some people saying my pet died of kidney disease, is there some mechanism by which public health - I don't think this is CDC work - could get that information.

DR. ACHESON: Yes, I think the mechanism would be that either the consumer would call the company and they would likely call us. And that would clearly register on both radar screens and it would raise a question, particularly with the heightened sensitivity and it would simply raise the question of whether there was a problem. You know, we've put things in place to minimize that likelihood. The import alert is essentially preventing any vegetable protein concentrates from China coming into the U.S. without being tested. So that reduces the likelihood. We have that domestic assignment going on doing a lot of testing and raising awareness. It reduces the likelihood. But your question is valid. If something does get in that we're not aware of, is there a formal mechanism? No. Is there a lot of informal through consumer complaint to directly to FDA? Yes, and I think we would -

DR. SHINE: Allen?

DR. ROSES: In an age where our food has a lot of the contents on the package and so there's testing done, wouldn't a preventive measure be to have mass spec or some surveillance on the import of - for a variety of products like this? This time it occurred with people trying to get around the nitrogen content which is what's measured, but perhaps in this day and age we should be using a little bit more than that.

DR. ACHESON: Yes. I mean, part of the new role I have is to look at what protections do we need to put in place, feed and food domestically and imported. And right now we're importing about 9 million lines of food into the United States per year. Now a line is a shipment. It may be a container-load, it may be a shipload. The resources aren't there to run every one of those through a comprehensive or even a simplistic mass spec process to look for what. You look for a bank of chemicals and compounds. We have screens like that that we do use based on risk. Melamine was not part of that cadre of things that we would look for until now, so as you move forward. But I think in essence the answer to your question is to put in place a risk-based

inspection program that's combined with prevention up front so we have a better handle on what's going on up front to try to prevent the problem, have that inspection intervention detection piece there so that you're using a risk-based approach to drive that based on all the information that you can come up with in keeping it nimble. And that actually - the key part of that is filling it in with what Dr. Woodcock talked about in terms of the bioinformatics of how do you handle data from 9 million lines coming into the United States on an annual basis in a way that will allow you to verify its quality, analyze it, react to it and so on in a timely way. So you know, your point is well taken of using modern scientific detection technology, but to focus it in on where we think the risk lies.

DR. SHINE: I'm going to interrupt the discussion. Please don't go away. I'd like to call on Carolyn for a moment to make some comments from USDA. We have some additional questions, but I think in the interest of the public discussion I'm going to just take an interlude here and both the Food and Drug Administration (FDA) and the public believe in a transparent process for

information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it's important to understand the context of an individual's presentation. For this reason FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group, their products, and if known their direct competitors that is likely to be impacted by the topic of this meeting. For example, this financial information may include the payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement it will not preclude you from speaking. Could I ask the gentleman who wishes to speak to come forward and to the microphone, and identify himself and consistent with this indicate whether he has any financial interests and make a brief

statement. Sir?

DR. PARKHIE: Mukund Parkhie, DVM, PhD, ex-FDA. I don't have any financial interest or any remuneration in connection with any of these companies. Regarding my question, first comment is that FDA has done tremendous job as far as time and all the regulatory agencies. You know, scientific aspect in this episode, widespread, wide from one species to several species. Regarding - a comment regarding Chairman's question, FDA Center for Veterinary Medicine has pharmacovigilance branch. If it happens that all of a sudden renal toxicity appears, a glut of reactions are all of a sudden, it will be marked, it will be known. There's no special department. At the same time, University of Illinois has got a toxicological center which filters all these adverse reactions also. Very nationally known.

One question I have to the audience or to the speaker goes to the toxicological pathology in feline, feline toxicity. And is the concentration of cyanuric acid and melamine, melamine as such if it is not toxic, interaction which forms the crystals, is it cyanuric acid and what is the concentration? Are there any

compounds with combines with melamine which precipitates the renal toxicity?

DR. SHINE: Thank you very much, sir. Appreciate your comment. Any other individual wish to make a public statement during the public portion of the meeting? Hearing none we delayed our break. What I'd like to do is to take a 15-minute break. We would reassemble at 11:15. At that point Carol may want to make a comment. We have a couple more questions and ordinarily we are not under an obligation to make an immediate response to a public statement, but if you care to respond to the question about the pathological - the pathophysiology in felines, please feel free to do so at that time. So let's take a 15-minute break and then reconvene promptly at 11:15.

(Whereupon, the foregoing matter went off the record at 11:02 a.m. and went back on the record at 11:16 a.m.)

DR. SHINE: Welcome back. Thank you very much. Just before the break Gail Cassell indicated she wanted to ask a question I think, but why don't we also ask Carol Maczka if she wants to make any observations from her perspective at the USDA. Carol?

DR. MACZKA: I just want to make two comments. In terms of surveillance which was brought out before FSIS does look at the kidneys of hogs going to slaughter, and of the 5 million hogs that were known to have been fed the contaminated feed only 235 of those hogs were suspected of having nephritis and of those only 15 were condemned which was no greater than baseline. So we do actively look at the hogs' kidneys going to slaughter.

And just one other comment. We are going to be working with DHS Centers of Excellence, FDA, FSIS, Customs and Border Protection to do a study of imports coming into the country and what other pathways could potentially be used to adulterate food for economic gain and see if those pathways can be piggybacked on to actually do, you know to do damage and what would be the consequence. So there is - a study of that is in the works to look at that.

DR. CASSELL: Ken, I was just going to share with you a conversation we had at the IOM last week in terms of thinking about surveillance issues for a lot of different things. And we were

discussing the fact that the rates of autopsies have gone so far down in this country over the last five to ten years in particular. And the other thing that David Corn really hastened to point out is that in the IOM report on medical errors that there was absolutely no mention of the use of autopsies, or how much we might improve on detecting those errors if there were more autopsies performed.

DR. SHINE: I would remind you that David Corn's original specialty was pathology and he at one time was responsible for autopsies at the Massachusetts General Hospital before he went on to bigger and better things, but your point is well taken. I have a few questions or issues that I wanted to raise. First, in your analysis you make reference to - that you've treated all four of the melamine and its derivatives, and you said assume that MC are equipotent. I wonder if you would elaborate on that, and I guess my concern is one about synergisms. That is, if the combination of melamine and cyanuric acid in fact has a particular effect in terms of crystal formation, then it's not clear to me that they are necessarily equipotent. It may very well depend

on the ratios of those and others. So help me understand the meaning and utility of that statement.

DR. HATTAN: At this point in time I think that I would only be speculating, but I happen to agree with what you've suggested. As a matter of fact during one of our conversations with our colleague from the EPA he said one of the test kits for determining whether you have an adequate amount of cyanuric acid in your swimming pool where it's used to support the chlorine compounds in disinfecting purposes is to take a little bit of melamine and toss it into the water and see how much precipitation you get. So you know, one's an acid, one's a salt so probably the ideal situation for precipitation would be if you had an equimolar mixture.

DR. SHINE: Is that true?

DR. HATTAN: I don't know.

DR. SHINE: I mean, it just seemed to me that that's not - I mean, that's I guess a relatively straightforward issue to look at crystal formation, look at the ratios and make some judgment as to what in fact would be a combination that would be particularly likely to

crystallize.

DR. HATTAN: The problem I think would be the influence, the potential influence of you know the bodily fluids.

DR. SHINE: But you can create a plasma-type environment.

DR. HATTAN: Yes.

DR. SHINE: There's a whole variety of - the only reason I'm stuck on this is that as you point out it takes enormous doses of melamine to produce a problem. It's still not clear to me just how much cyanuric acid it takes to create a problem if you have a lot of melamine around.

DR. HATTAN: Yes, that's true, but if you look at the comparative toxicities of like melamine and cyanuric acid as sole individual agents, cyanuric acid appears to be even less toxic than melamine.

DR. SHINE: Right. So again it's a synergistic, or an interaction. Secondly, as you point out melamine is not particularly metabolized in the body. The presumption is that there must have been bacterial exposure of the melamine at some point I would guess. Do we have any notion as to where and how that might have taken place,

or whether there are other mechanisms by which one would get these breakdown products that might be relevant to other exposures of melamine?

DR. HATTAN: I don't know how reliable this source is, but I think both the Washington Post and the New York Times talked about reporters in China who had talked to some of these pet food manufacturers and they claimed that they went to the chemical plants and just bought the leftover chemicals, this type of chemical from the chemical companies and then included it in the food. Now all of this you know totally is hearsay, but I think that it could explain why there is this mixture of chemicals of this. You know, they're all the triazine class, but there's a whole spectrum of different structures. It's the kind of thing that you would see from side reactions or leftover products from a chemical production process. And what they call it is buying the scrap from the production process.

DR. SHINE: So you think that the most likely - or you didn't say that. You said the newspapers were reporting, but the speculation is that it's actually in the chemical production as opposed to breakdown?

DR. HATTAN: Yes, but I think as our colleague from CVM would support, there are bacteria in the gut, especially in ruminants that actively break down melamine to all of those molecular species that we described.

DR. SHINE: I mean, obviously one could make a career studying melamine and all the various aspects of it, but this is along the same line as Lonnie's question about heating and resins and so forth is that the more we could learn about how you end up with this combination of medically unproven ingredients would be interesting.

This is more a question for Dr. Acheson. What you've told us is that manufacturers were importing into the United States something that they called wheat gluten or rice gluten and that in fact it wasn't what it was purported to be, it had relatively little gluten in it compared to wheat flour, substances were added to it which would increase the nitrogen measurement that you get from that. I'm not a lawyer, but that comes very close to my mind as fraud or misrepresentation, and I'm wondering whether you or the agency has looked at that aspect of this in terms of whether in fact this is

illegal behavior in terms of false labeling. You made the point that the melamine may be helpful in terms of creating the pellets, and I would have found that a compelling argument if it had actually been rice gluten and wheat gluten, but in fact it wasn't that either. So would you help us with regard to this aspect of this adventure?

DR. ACHESON: Well, first of all let me clarify. The pellets that I talked about, that was the material that was manufactured in the United States as fish feed and animal feed. They were pelletized and our understanding was the melamine was added there to assist with binding and pelletization. That was different. The - what you're referring to in your first set of comments was to do with the imported product.

DR. SHINE: That's correct.

DR. ACHESON: Our Office of Enforcement and our Office of Chief Counsel are indeed involved in looking at this to determine whether some of the things that you suggest have merit and what to do about it. That part of the investigation is continuing and I don't think any decisions have been made along the lines of any criminal component. We really sort of treat that

separately from the public health piece and I'm primarily representing the public health piece, not the criminal part. But it's definitely something that is on FDA's radar screen and they're certainly pursuing that angle to see what could and should be done about it.

DR. SHINE: And I heartily support the separation of powers here in the sense that you worry about the public health and they worry about the enforcement part. On the other hand, the enforcement part ultimately will turn out to be very important in terms of whether people actually provide us what they represent to provide us.

Allen Roses raised a question of mass spec. We've agonized about the fact and correct me if I'm wrong, that probably less than 1 percent of food that's imported into the country actually gets examined or tested in some way.

DR. ACHESON: That's about right.

DR. SHINE: What are the lessons learned from this experience with regard to protecting the food supply? You very appropriately talked about prioritizing risk and trying to identify where the greatest risks are and focusing attention on that. I'm impressed,

maybe you could remind us of the exact number, but the number of food inspectors that the FDA has for examining food given the 9 million lines that you talked about is a rather small number. Should there not be some lessons that we take from this in terms of some urgency with regard to improving our capacity to identify and follow up on high-risk products that come into the country? And with all due respect to China, between toothpaste and protein it raises a lot of questions about anything that's coming in from that part of the world.

DR. ACHESON: Well, you've raised a lot of very pertinent points in what you've just asked me. You started out by saying lessons learned, what lessons learned have we got from this situation and I think one of the - there are several. The risk-based approach is what we have been using. It's what post-9/11 was the basis of the Prior Notice Center which essentially for those of you who aren't aware of it is the system that was put in place post-9/11 which requires anybody who wants to import a product to have to inform FDA. It's run through an electronic screen. If anything jumps out from that is of

concern the product is inspected and potentially tested.

I think what this tells us is we need to be thinking even further out of the box as to what constitutes a high-risk product. You typically think of risk of those products that have been associated with illness, products that come in that are not subsequently heat-treated or cooked with regard to a pathogen at least. This tells us that we need to be thinking along the lines of well, are there products that may be coming into the United States where there is some economic adulteration going on, or an adulteration going on for reasons of economics that potentially could constitute a public health threat. And that gets - the lesson learned for me on this is to think outside this box of risk defined narrowly. You've got to broaden it further and further.

Now, you also mentioned well, where does China fit into this. We have to look at this in the context of our current regulatory authorities and that is focused on if you inspect something, you test something, you find a problem, you can do something about it. You know, we put import alerts out early here with regard to

specific companies. It began with the first one, extended to the second one with the rice protein concentrate, then it became countrywide. And we've done that with other things. I mean another good example of that is in relation to fish, imported fish in relation to antibiotic residues and antifungal residues and other compounds. There are several import alerts in place focused on certain companies, manufacturers importing contaminated fish into the United States. We're not in a position to simply say we need to shut down any one country's imports just across the board. I mean, we don't have the authority to do that.

DR. SHINE: Nor am I suggesting that.

DR. ACHESON: I realize you're not suggesting that. So what the requirement here is to focus your risk thinking not just purely on the product, but to broaden it to - and it may be that you know fundamentally, a country that has a solid, strong, longstanding food safety infrastructure is less likely to have a problem than a country that doesn't have that. So then maybe that needs to be part of the risk strategy thinking of should you put more emphasis on this

inspection with the limited resources, and you asked how many inspectors. There's approximately 500 or 600 that do food inspections at various times. It is about 1 percent of imports. It is risk-based, but that means that there's a lot that are not being inspected. Now, I personally don't believe that doubling, tripling the numbers of the inspectors per se is the answer here. You've got to focus it based on risk and I think to get to Dr. Roses' point, you need modern detection technology so that you can focus the risk, you can do the test and you can do it quickly. And that's something that we're looking toward doing.

A second lesson learned, because all that I've spoken about is really food safety. A second lesson learned here which is also important is the potential vulnerability of the food supply to deliberate attack. This was obviously a deliberate contamination with a compound for a specific reason. I think what that illustrates is that it's certainly possible to contaminate a product with a compound that could be imported that could go into widespread distribution, it could be used in an ingredient in many foods and potentially result in harm to humans. I think we

- this was a - this obviously went to pets. It could just as easily have gone to humans and as we discussed earlier, I don't know whether we'd have seen the health impacts in humans because of the difference in physiology, but you know it simply illustrates that point. So this does require further thinking about deliberate attacks and vulnerabilities from imported products.

DR. SHINE: Thank you. One final just minor point. You had indicated that the original methodology for measuring these four substances in food had been published and is widely used by companies that choose to examine their products and so forth.

DR. ACHESON: Yes.

DR. SHINE: The methodology for identifying the agents in hogs, fish, is that also published?

DR. ACHESON: Yes.

DR. SHINE: So that's all available?

DR. ACHESON: Essentially they, and I don't want to misrepresent this. There was not a published method prior to this episode.

DR. SHINE: Right.

DR. ACHESON: Once we had developed the

method - and it began just with melamine in wheat gluten and pet foods. It then extended to the other compounds. It then extended to the fish and the shrimp and the chicken and the hogs. As those methods have evolved, the website has been updated to reflect the availability of that methodology.

DR. SHINE: Good. Any other questions? Yes, sir.

DR. SASICH: Just back on the crystal formation with the melamine. One of the slides mentioned diuretics. Was that a theoretical consideration, or did you actually have information from pet owners or from vets that animals had been using diuretics?

DR. HATTAN: At this point as far as I'm aware it was entirely theoretical.

DR. SASICH: Would it be worthwhile in a situation like this to go back or to look back to see if these animals were taking other drugs? There's a similar kind of requirement in human beings when there's an adverse event reported that the manufacturer or the producer has to exercise due diligence to find out as much information as possible for the agency about a particular patient, or in this case a pet.

DR. ACHESON: Let me try to address that. You're asking a very good question. Part of the lesson learned here is when this situation happened we got swamped literally with calls. I think it was on the order of somewhere between 15,000 and 20,000 calls from pet owners who were concerned that their animal had died as a consequence - or got sick as a consequence of exposure. Now, the difficulty there is that renal failure in a cat or a dog as a cause of death or a cause of illness is not that uncommon. I'm not a veterinarian, but I know from personal experience and talking to veterinarians, you know that's a common way for elderly animals to depart. So you know, is it coincidence? Is it directly related to the pet food? But there was a lot of calls, and part of the logistic difficulties was just simply handling those to ask the sorts of questions that you're addressing which clearly could help indicate what constitutes the higher risk and what may be leading to the crystalluria and the renal failure. So we're certainly not there yet, but it's a valid question to ask.

DR. SHINE: Other questions? For the members of the board I call your attention, at the

very end of the first section of the melamine release is the charge to the board with regard to this issue and you might take a look at it. Let me summarize what I think I have heard and what I would propose to represent, if the rest of the board agrees, our reaction to this situation. First, the board is pleased with the speed, care and effectiveness with which the FDA approached what was a very rapidly emerging problem which initially started out as a challenge to pets, but rapidly became a question of the safety of the food supply. We are very pleased that from the earliest stages of this activity that the FDA collaborated very closely with other agencies, including USDA, CDC, HHS, in some cases the manufacturers of foods and that that collaboration was effective, collegial and successful. We concur in the overall results of the risk analysis that the probability of harm to humans from ingesting fish, poultry, pork from animals which might or might not have been exposed to feed containing these contaminants or these substances, that that decision to - that the risk was low was an appropriate decision and we concur with the FDA's decision to allow the sale of those foods

and to allow that material to enter into the food supply. We are impressed with the quality of the scientific expertise which the FDA brought to this problem, including the development of new methods for measuring these four substances, both in feed and later in food products, and we were particularly pleased that the methodology was made available to the community more broadly such that at least in one case, perhaps in several, the discovery of contamination of a product was determined by a company using this methodology.

I think the committee believes that there are important lessons that have been learned from this experience as articulated particularly well by Dr. Acheson. Among them is the notion that one may very likely need to broaden the criteria for how one evaluates risk, and those criteria may have to include a number of variables that heretofore have not been part of our risk assessment approach and that that is a work in progress that we would want to follow carefully. I think we also concur in the observation that he made that the deliberate introduction of a substance into our food supply is a real risk. In this case, not via terrorists but that under other

circumstances the malevolent behavior of some forces could in fact introduce serious threats to the food supply for which we must be very alert.

We were very pleased with the quality of the peer review even though a couple of the members came from the Science Board. But we thought that was a very useful methodology for rapidly helping in the assessment of a public policy issue, and commend to the FDA in the future the notion that if we have important issues of this kind that we reach out very quickly to the scientific community for the appropriate kinds of consultation in these matters and that as someone suggested, the involvement of such interested people may in fact be a transition by which questions raised by the risk analysis could ultimately become research questions on university campuses and in industry. We recognize there are limited capacities for doing research in response to this episode, but we are particularly interested in efforts which, one, would enhance, improve the analytical methodology that could be available for problems of this kind, including those that involve compounds from the family of triazine pesticides, that species differences in

susceptibility would be of considerable interest. Although we recognize that this was an acute event so to speak, the concept that there might be situations in which low-level chronic exposure was a problem suggests that some additional investigation of how and in what way that kind of exposure might occur and what its consequences might be would be important, and that different kinds of effects which would increase the production of byproducts, including heating, cooking, things of this sort, might be important areas for investigation.

The board is very pleased with the outcome of this process. It would, however, like to have a follow-up either in its fall meeting or early next year in which Dr. Acheson and colleagues reports back as to, (a), which of the research initiatives in fact were followed up and recognizing that not all of them can be, but recognizing that some priorities have to be set, but that this is an important enough issue that we would like to have some follow-up. Secondly, and this is my own opinion, I would like to find out what the agency determines with regard to whether there were any legal implications of this,

although again we strongly support the intensity of the effort to protect the public health quite apart from any of those legal issues. And we would like just a very brief follow-up as to whether there is any evidence for this or any other problem with the food supply as it relates to pets, or the introduction of glutens, both wheat and rice, into the United States. And finally, if as a consequence of the review of the report there is a change in how and in what way the priorities for surveillance are modified, to the extent that you're comfortable in discussing them in a public environment we'd be interested in knowing how and in what way that would be done. Are members of the committee reasonably comfortable with that summary and do you want other, added, subtracted? Allen.

DR. ROSES: I think it's terribly elegant and one of the things I'd like to suggest - maybe Gail can facilitate this - is that the conclusion so this be circulated through the whole subcommittee looking at FDA science. Because it does answer in a very practical, elegant and superbly well done way some questions that have been asked by some of our outside consultants.

DR. SHINE: Very good. Other comments? Again, Dr. Acheson, Dr. Hattan thank you very much. We recognize this was - Carol, thank you - that this was not a solo act. There were many, many other people involved in this, but I think this is a good story, it's an important story and hopefully will not occur too often, but again if we can follow up from the lessons learned that will be an extremely valuable outcome.

If there's no additional business, we are free now to go to lunch and we will reconvene - let's see. We're actually, believe it or not, 15 minutes ahead of schedule. Is lunch available for the committee right now? With the forbearance of the committee and of Lonnie since he's going to make a report, suppose we came back at 12:45? Get a jump on the afternoon for those people who have to catch airplanes and so forth. That okay? We will reconvene at 12:45. Thank you.

(Whereupon, the foregoing matter went off the record at 11:47 a.m. and went back on the record at 12:51 p.m.)

DR. SHINE: Ladies and gentlemen, if we could reconvene we'll get ready to begin the afternoon session. Periodically as you know we

undertake a number of peer review activities. Today we're going to get a report from a committee chaired by Lonnie King on the review of the National Antimicrobial Resistance Monitoring System program, NARMS, which is an important and actually very interesting program again because of its involvement of multiple agencies in terms of performing this very important function. Lonnie, would you give us a precis of the report and then we have a chance for some discussion and questions.

DR. KING: Sure, I'd be glad to, thank you. Rather than to stand there with half of the crowd behind you and half in front, or less than half, if you don't mind I'll do it from here. If you can't hear me let me know, otherwise we'll just do it from up here if you don't mind. So thank you for the opportunity to report on the project review that we have completed. And before I start, you have the handout available to you which is the full report and the review. It also has in there a listing of colleagues that were involved in doing this review. And Susan Harlander and myself were part of the board that were engaged in this, but I want to thank and also

acknowledge colleagues that were part of this review. It was an outstanding group and they are listed as well as their bios for you to take a look at.

So this is the National Antimicrobial Resistance Monitoring System, or NARMS, program review. The charge to the committee was the board, Science Board advisory committee to FDA established a subcommittee which we did the work to evaluate NARMS program and address four critical questions relevant to the continued success of the program. These are the four questions that came out that we especially focused our time and attention to. The first one talks about inherent bias samplings in NARMS and improvements that are needed. The second are about epidemiologic or microbiological research studies that would better serve the goals of NARMS. The third are about methods to take a look at data harmonization and is the level of reporting and timeliness of the reporting appropriate for advancing the goals of NARMS, and are the current NARMS international activities adequate considering the growing worldwide problem in antimicrobial resistance. So those are the

four questions that were posed to our subcommittee.

The approach was kind of typical that you see on other reviews in terms of this group coming together in Rockville on April 10 and 11. We heard presentations from first of all an overview of the NARMS project from each of the three arms if you will of the participating federal agencies. Also, part of this, our process was an open public meeting so we did hear from five or six people from the public that had comments and also presented data to us. So we reviewed all of those multiple reports, past reviews and studies and other analysis before the meeting and during the meeting as part of the process. I hope, I assume that most of you know about NARMS, but a national collaborative network involving CDC, USDA and of course FDA. The system was developed to monitor changes in susceptibility and resistance of select zoonotic bacterial pathogens and commensal organisms recovered from animals, retail meats in humans to antimicrobial agents of public health and of animal health significance. NARMS was started in 1996 in response to a public health

concern based on the recognition of a growing problem of antimicrobial resistance. This is the goal of NARMS and kind of four points that have been summarized: to provide descriptive data and trends on susceptibility and resistance of zoonotic food-borne bacterial pathogens and select commensal organisms; to respond to unusual high levels of resistance whether in humans, animals or retail meat; to design follow-up epidemiology research studies and to assist the FDA in decision-making for approving safe and effective drugs for human and animals as well as promoting prudent and judicious use of antimicrobials.

So as the subcommittee read the reports, talked to each other and listened to comments both inside these organizations and outside, these were some of the general themes that came forward in addition to our responses and findings for the four questions. One was that there is no question that we believe a need for improved sampling strategy, and that was actually the first question that was proposed to the group. We believe that there's a need for the timeliness of reporting and issuing reports, that they need to be closer aligned to actual data-gathering.

Harmonization of data and results are critical. Heard a little bit this morning about bioinformatics and FDA, and kind of the big approach about how FDA is looking at this. I think this is a microcosm of why that's needed. The creation of a contemporary surveillance platform. So there's standardization where there's more utility of information and data as we move ahead. And I would say that the group, our subcommittee strongly understood and endorsed the idea of this being a very high priority for future support and attention. I'll talk a little bit more about this as we go through this. And we believe that - one of the findings was it would be good for the partners of NARMS to look for potential partners and other sources of funds perhaps as the system moves forward. While this is primarily a public health system and strategy, I think it's underappreciated sometimes for the benefits to meeting the needs of veterinary medicine and veterinary and animal health clinicians. So they are not well served if they have antimicrobial agents that are resistant and not working well, and we think that that needs to be a more apparent part of the strategy. Without

question though there needs to be a continuous focus on public health impact and always going back to the question about the public health impact about what's being done here. And there's a concern, both at the public meeting and within our subcommittee of some limitations to NARMS based on the lack of drug use data available to these groups.

So we take a look at Question 1 which really focuses on potential inherent biases to the sampling strategies. So in this first question our findings were NARMS really started as kind of a sampling strategy based on convenience if you will and I think it's evolved over 10 years or more to necessity to be able to withstand the scrutiny of further scientific and regulatory purposes that are being applied to NARMS and the importance of that. The sampling really has kind of three different strategies. One is human samples. They come from state health departments, partly from FoodNet surveillance systems. There is variability in these different departments that are part of the bias. There are samples being taken from patients that are coming in due to treatment failures which is a source of bias and

it's pretty much a passive system except for some of the FoodNet sites. So one of their findings would be that we believe to have a truly national randomized sample it would certainly help with the utility of the information and the ability to make further inferences. And we would suggest that there be further stratification of the data that's been collected in the samples to help identify transnationally and perhaps even doing some periodic active sampling, or active surveillance work in clinical labs, realizing that there's still some bias because of what samples physicians would send into the system. We also believe as a finding that it's important to have isolates that are analyzed from intestinal flora of healthy individuals. While some of that's being done in NARMS, we understand that there's great kind of gene fluidity if you will between the bacteria of interest here. And some of the sampling now for intestinal flora of healthy individuals don't really come from healthy individuals at all. So these are some of the biases that we've seen and some of the findings that we would move forward for consideration.

In terms of retail meat, the

methodology has certainly undergone a series of revisions that have improved this, but the sample's still small and if you stratify it it's further reduced and kind of limits because of the limited products and limited areas in which this is done, making for probably difficult interpretation. There's some pilot projects in terms of an Iowa study, et cetera, that show some real promise in terms of kind of expanding this. So our finding was that it would be helpful to design a statistically valid national system. We realize that that can be costly so an alternative strategy would be to actually look at more hypothesis-driven studies. So start with the question in mind, design the strategy then around answering the question if you will, and these have to focus on further understanding of the sources and risk factors of resistance.

In terms of the animal component, three sources, HACCP implant sampling, clinical diagnostic laboratories and the National Animal Health Monitoring System on farm sources. We also found sources in - bias in these kinds of sampling strategies as well, but we also understand the need for kind of taking samples that are available

as the system moves forward. So the implant HASSP sampling is probably not reflective of a true randomized sampling because of the overweight if you will of sampling from processing plants that are probably out of compliance. So we would hope that there might be consideration given to adjusting HASSP sampling methodology, or perhaps even adopting a baseline sampling scheme that can be used that would be more representative of a national database. The on-farm system is here again not really truly statistically representative or valid of U.S. farms. I think it's an important addition to NARMS and what it's done. There was particular interest in a system called the Collaboration in Animal Health and Food Safety Epidemiology which is a sample that looks at both diseases and microbes on the farm, and I think more could be done with that and we see some real upside potential to look at that. Here again on these samples, perhaps considering an hypothesis-driven sampling approach would be the best way to go. The clinical diagnostic labs have inherent biases and certainly - but could be used as a component that would look especially at early warning systems through that kind of sampling

strategy.

The second question had to do with epidemiological or microbiological research studies to better serve the goals of NARMS and the regulatory work done by FDA. Findings talk about as you see there a further expansion if you will of the current program's research portfolio. That would be to continue to consider standardization and new laboratory methods, platform development and the use of more pilot projects that would enhance the goals of NARMS. And here again as kind of a fourth part of this we think it'd be important to expand the hypothesis-driven research with a special emphasis continuing to look at an assessment of real human risks if you will. We need to think about, would hope that the group would think about expanding methods development that would detect the resistant genes, whether they're in fecal samples, or carcass samples, or food samples without regard to bacteria, but start really looking and shifting analysis unit from the organism to the gene level. And to encourage more collaboration and partnerships. These are critical data. They're becoming even more important. We realize there's some

confidentiality issues with sharing these data sets, but we would encourage more collaboration, especially with university groups, to add value to this data in terms of further studies, or even NIH as a partner that could consider research and perhaps more funding into this area. We really need to rely on the NARMS system to help us gain an understanding and a focus of this complex flow of resistant genes or bacteria across the farm-to-fork continuum. It's about infectious disease ecology, the complexity of events that need to take place and we believe that NARMS is positioned to really help us understand this complex set of events and hopefully future interventions and prevention strategies.

Third question talked about data harmonization and asked the question about the appropriateness of the current reporting, and are there better approaches to use or to consider. So there's a critical need for a realtime integrated database for all three components of NARMS. I think that also came out today. It's easier said than done I understand, but it may be part of the overall IT solution that FDA is talking about that we heard about this morning. There certainly has

been a lot of very good work done in the harmonization and standardization of microbial techniques and methods. We think the same kind of rigor if you will now should be approached to an IT solution to how to handle these data and make them more accessible. Such a system needs to rely on defining the attributes of what needs are and not based on adopting a strategy or hardware and software system that we have to fit our attributes into. So a web-based off-the-shelf solution would be ideal if possible.

NARMS still should have separate reporting from the three groups because of areas of interest and stakeholders, but we need to develop interfaces of these three groups and the ability to summarize data collectively across all of NARMS. Needs to be more accessible where other researchers can add value and realize that there's some confidentiality of data here, but we believe that the right system in place can actually protect those kinds of data sets and still be able to use them by these three agencies. We'd encourage more scientific publications and broader types of reports and analyses supported by the idea of an integrated database system. We

certainly encourage and it certainly came out in the public meeting more drug use data to be a part of the analysis that needs to be done at NARMS to kind of move it forward. There's limitations to the usage because of not having those data sets available to the group.

The last question really focused and talked about the need for international activities, should the be expanded, what's the collaboration like and this is a growing international problem. I think there's no question in the subcommittee's mind that we strongly would endorse continuation and expansion of a global activity in looking at antimicrobial resistance. The data are there, suggest more imports from overseas and perhaps from countries that don't have nearly the rigor in their system that we do and the exposures of people to resistant organisms. So better coordination of NARMS components looking at all three individually and collectively in terms of their international utility. And while other countries are doing this to a certain extent we think NARMS can actually be the global model and probably should be.

To make sure that we adapt new

technology that could be considered as an international system that would ensure good quality of data reporting, the group suggested that there should be kind of a single person or position or spokesperson that would go forward in international settings and represent NARMS best. And the very important role currently done in NARMS in a minimal way and that's to look at continuing expansion of global training. So if we have expectations for greater global interest and training, then we're going to have to do more of that.

The final findings and kind of suggestions in addition to looking at those findings from the four questions would be the subcommittee was especially pleased with the commitment and the dedication that we found with the NARMS team. And for three very different cultures from different government agencies to come together over the last 10 years and this kind of commitment and dedication and collaboration was something that we found to be most laudable. Outstanding progress has been made over the last decade and a very positive acceptance of NARMS and what it's trying to do. The question didn't come

up is NARMS necessary. The question came up I believe that that's already understood that it is. It's the improvement of the system and the utility of the data for contemporary uses.

So when we looked at kind of the evaluation of the program we see NARMS as especially looking at improving what is. Kind of incremental steps over the years from better methodology and kind of step by step expansion to one that we think that we now need to look at creating what isn't, an opportunity to look at NARMS at the next level. And they've kind of passed the test. They have moved into I think a position now where with goodwill and the work that's been done they really need to step back and look at a potential 10-year NARMS plan for the next decade ahead. And this would suggest a visioning and strategic process perhaps with business planning to be adapted to do that with a lot of public input. And we think that this program can evolve a lot more to become more predictive, more responsive, certainly more expansive and would endorse kind of a 10-year program development as NARMS moves ahead with its public involvement to really look at the new

possibility of horizons of what's needed, considering the contemporary issues and problems that we see. So animal agriculture and the global food system and public health have a great deal of complexity and the understanding of infectious disease ecology and how these groups and processes come together to create new problems and issues would mean that we need a program in NARMS that was practical and one that could address these contemporary problems in a more involved complex environment and a greater national need. Dr. Shine, I'll kind of stop there and I'll ask Dr. Harlander who was also part of the subcommittee if we can address any questions. Susan, do you want to make any comments?

DR. HARLANDER: I just have a couple of comments. The first is I was charged with taking notes on the public comments and I was quite impressed that from a very diversity of audiences that included trade associations that represented the regulatory agency as well as trade associations that represented animal producers and processors. We also had a charitable organization that promotes better methods of raising livestock and poultry, an association dedicated to promoting

proper antibiotic use and a science-based non-profit advocacy group as well as academicians. And there was pretty consistent support for NARMS across that, and I think that's one of the first times I'd participated in something that that diverse an audience had such a consistent message. And I thought that was actually quite significant. The other two things, and Lonnie has mentioned them, is that some stakeholders would have pushed the subcommittee much farther to the point of requiring the reporting of antibiotic use in order to couple that with the actual data that's coming out. And another significant group to incorporate a recommendation on increased funding, or at least long-term assured funding for NARMS. That was outside of our charter, but you'll see that a couple of those themes did come through in the report as well.

DR. SHINE: Thank you very much Lonnie and Susan for your very good work on this project. I also would note that Jim Riviere and John Thomas who have just recently gone off this committee participated in the review as well as two or three other outstanding experts. I found

the report to be comprehensive, thoughtful and insightful, and there were a number of recommendations which I think were rather important. I would echo Susan's last - Dr. Harlander's last comments about the resource issue in terms of how much and what can be done and what ought to be done under these circumstances.

Let me begin the discussion with a few questions. First for either of you, who should be the audiences for this report? The report comes to the Scientific Advisory Board, but in terms of having the maximum impact from your analysis, where do you think the report ought to go?

DR. KING: First and primary to the NARMS partners as suggestions for them to continue to improve the system and to move it to the next level, but I would hope that it would have a much broader public viewing. This is a growing public health problem and frankly an animal health problem, and I think the NARMS program, what it's done and what it's capable of doing should be considered by a larger group of people. I think it has evolved into an almost mission critical program for FDA and I think that more people need to understand it and be supportive of it, and I

agree with Susan that we think that this should be a very high priority in all three of these agencies. A diverse group of stakeholders really needs to look at it and help determine its future.

DR. SHINE: So this would include in addition to the Commissioner of the FDA and the Director of the CDC the Secretaries of Agriculture, Health, the various groups that testified before you in terms of the interest groups that were involved. I think it would be helpful, Lonnie, if you and Susan gave some thought to any other, in addition to the general statement that you've just made, any other audiences because I think this is the kind of interagency, interdisciplinary activity that deserves wide dissemination. And I think even though it's been organized at the Science Board, we really need to make sure that it gets out to a lot of other folks. Are there scientific advisory boards at these other agencies, for example, that should receive a copy of it? Where are the other levers if you will in terms of understanding what's going on?

Second question. I was struck by the problem of - I think at one point you described a

4-year lag in the collection of data and their release. And you urged a much more prompt reporting process on the basis of what is collected at the present time. Can you put a target on that? What should NARMS be aspiring to in terms of a reasonable period to collect data and then to make it available to the various constituencies?

DR. HARLANDER: Right now because of some of the IT issues I think getting all of that information being able to be entered into a common database would almost give you a realtime capability if that existed. And having a 4-year lag, I think this is the first written report that's come out from NARMS, a collection - it's basically a collection of information, and to make decisions about changes in antibiotic use, that lag is significant. And so a lot of it focused around an assessment of the IT capabilities and the ability to have some common way to get that information into a system that could be ultimately searchable, and ultimately available to -

DR. SHINE: Your proposal is for a if you will realtime - essentially continuously available data source. Is that what you're

saying?

DR. KING: Ultimately that would be what - that should be the endpoint that we should move toward. And if you really go back and look at the goals of NARMS, you know one of the critical goals is to improve decision-making. You can't do that if you have that kind of a lag between data collection and report consideration.

DR. SHINE: You made the point in the report and in your presentation about the issue of getting reliable data about antibiotic use and some reluctance to provide it. This is - I mean, this may be absurd, but just one thought. The Institute of Medicine publishes every few years a chemical codex and it gets proprietary information from companies all over the country which is quite accurate and complete, but is held in complete confidence. And so they're willing to provide that information because the IOM is seen as a neutral collector of such data and protects it from disclosure. The question I wanted to raise was, one, you can try to regulate this kind of thing. I think you said someone suggested it, but the other possibility would be to have some kind of trustworthy intermediate if you thought that

would be useful. So I just wanted to see, again, not knowing all of the - that may not work, it may not be practical, it may not give you the information that you need and so forth, but I just wondered what you thought about exploring something like that as an intermediary step.

DR. KING: I think that certainly is a good suggestion. There's some data available in terms of kind of bulk use of antimicrobials, but it lacks the specificity to really start looking at cause and effect relationships. So if there's a third party as a broker that could help I guess add the confidentiality to this I think that would be an important maybe next step. The same thing's happening with on-farm data where there's problems with producers signing up because of - they believe that this data can't be confidential. It's FOIA-able and that really needs to be addressed I think and we won't even come close to you know a national survey until we get those on the table and resolved if possible.

DR. SHINE: You make reference to the need for a contemporaneous surveillance platform. Would you elaborate on what you mean by that?

DR. KING: I think it goes back to the

utility of the data, the idea that there's a standardized format that can be used for all three of these agencies in terms of data collection and that can be integrated together as kind of a national surveillance platform. So it's one that isn't customized just for CDC or FDA or USDA, but it's one that can be generalized if you will was a composite. So we would call that an architecture or a platform then that could - that would have greater utility.

DR. SHINE: And finally this may or may not be an unfair question, but given resource limitations and so forth, if you were to identify you know one, two or three of the highest priorities that you see for NARMS to try to confront over the next several years, you've talked for example about the importance of a 10-year plan, but you've also talked about a lot of other needs. We're going to obviously ask NARMS to look at this report and to make comments about it, and they obviously would also have notions about priorities, but I wondered if you would be willing to say given the breadth and scope of these issues that you think that in the next three to four years it's urgent that one, two, or three

be done. Is that unfair, or can you respond to that?

DR. KING: It may not be unfair, but it may be something I'd think about a little bit longer. I think the questions actually kind of framed us I think number one, you know, to move this into more of a national sampling with less bias so it has greater utility would be an important step. Certainly the IT solution - ability to have more realtime, an integrated database system would be high on my list because it adds to the utility of the data and the ability then to use it for improved decision-making. And although the subcommittee would not like to see resources that are constrained used internationally - we'd rather use them here to get this system into its next step - the idea of expanding this into a global model, developing more international partners because we believe that's going to be a critical part of the future problems of antimicrobial resistance would be up there as well.

DR. SHINE: Thank you. Susan? Good. Are there questions, concerns from other members of the panel? Dr. Cassell. This panel.

DR. CASSELL: Gosh, I have a number of things that I'd like to say. First of all, I think it's a very good report. The one thing that has concerned me for a long time has been the fact that regardless of what we do in this country, unless we have a better handle on the international scene and the ability to have some impact on the policies put in place on the international scene, we will be compromised for all the reasons that we know. I was really disturbed recently. I made a point to go to WHO about six weeks ago to find out you know what they really are doing with respect to antimicrobial resistance. Back in 1995 when the ASM issued our report on antimicrobial resistance at that time WHO was spending less than $100,000 a year on monitoring antimicrobial resistance. This year when I went what I learned is that there's no longer an organized group formally charged with antimicrobial resistance, TB for example. You have MDR TB, XER TB, but that's not tied into the overall you know issue of antimicrobial resistance which obviously it's unique in some ways, but certainly in some ways not. So I guess the real question that I have is Lonnie, you mentioned the

FDA or NARMS being the global model, but do we think that the other countries really see us as the model anymore and aren't a lot of decisions being made necessarily or unnecessarily without significant input from the U.S. in this whole area? And if you had to pick a country where the data-gathering are better, i.e., less biased than say perhaps what we perceive it to be in this country, which country would that be? Who would we pattern ourselves after?

And then, you know gathering the data in terms of use of antimicrobials in humans is one thing, and I think we can do it very good. When we start talking about monitoring use in farm animals, in catfish farming, et cetera, et cetera, it becomes I think almost to me anyway overwhelming in terms of how do you do that, how are you sure that it's reliable and if you - even thinking about you know regulating reporting, you know what about compliance, and how do you gather the data, how costly is it going to be, and the bottom line is how will we use the data once we get it and will it change anything that we're currently doing to make different decisions.

And then lastly, it seems to me again,

and I haven't followed this closely, but a decade ago you were already beginning to see the trailing off of development of antibiotics for human use for a lot of reasons. And we all know, those of us who are in the business of discovering drugs that a lot of the products, antimicrobials for animal use really were spinoffs or fallouts of the drug discovery for humans. Now that we don't have that going on, what kind of drugs, antibiotics are in the pipeline for animals and if we do significantly reduce the use of antimicrobials in animals today, what would the implications for animal health be? Do we have any data on that, or who will do the research to kind of predict what the impact might be, whether it would be adverse, or we won't see any difference? I don't really know.

And also, as far as your report, did you talk to stakeholders, did you talk to the other members that have input into antimicrobial surveillance, the interagency task force, you know what does USDA have to say? I guess did you check with professional societies that would be impacted you know by your report in this area? I was thinking when Ken asked the question what about

the audience, I would think that the American Association for Veterinary Medicine, the schools of veterinary medicine, American Society for Microbiology. I mean, I can think of a number of professional societies that it would seem to be - this kind of information is very important to them. And it would be very useful I think if there were some way to get input from those groups you know with respect to the report, or maybe just at least make them aware that the review has been conducted and you know hear what the results are. Those were my main thoughts as I looked.

And then as far as the IT piece, Lonnie, this is where I would hope that it will be possible if you would take this responsibility to share this part in particular with Dale Nordenberg because he is at CDC as you know, but serving on the FDA Science Review Committee and it would be great I think to have some conversations with him about where you see the needs.

DR. SHINE: Do you remember all those questions, Lonnie?

DR. CASSELL: Well, more comments than questions.

DR. KING: I wrote them down. That

sounds like the 10-year plan Gail, but just a couple responses, and thank you for those. I think they're right on. I think at some point I would hope to be able to see a system in place where products might be differentiated based on consumer's ability to understand about production systems and products, and rather than just rely on a stronger regulatory environment. There actually needs to be more done in terms of public-private partnerships and this burden doesn't have to be borne just by regulatory or federal agencies. And I see certainly responsible industry groups coming up that certainly understand that and are willing to I think play a greater role in that. The advent of WTO and what's happening in terms of - international standards in terms of trade really puts us at a different position in terms of our ability to lead.

DR. CASSELL: Is that a leadership position or not?

DR. KING: Well, I think some European countries have done you know a good job, but I'm not sure that those are really fair comparisons. When you look at our you know agriculture animal system and the number of animals that are

slaughtered here and exports versus a small country, it's like comparing a state rather than a country to what we're trying to do here. I do take to heart your idea about what we're going to do in animal health. I think that this is very much a public health system, but I see a little bit of an unevenness if you will in terms of the benefits of animal health, and I would like to see the veterinary profession be more involved. And certainly with Dr. Sundlof at CVM and others there's been a movement toward more judicious use of antimicrobials on the farm, even starting in veterinary schools, starting to understand that. But I think that they're kind of an uneven partner at this point and I think if there's more benefits to them. They have just as much to gain or to lose if you will, depending on NARMS and really what happens. So I'd like to see them to be a more effective player.

And then I think the idea of perhaps it's time for a national forum to take what's been done over the last 10 years, what's been found in this review into a broader audience to talk a little bit about what Dr. Shine talked about, and bring this forward and talk about what else should

we consider here if we look 10 years ahead. Where would you put the priorities on this? Who are the beneficiaries? Here's some changes recommended, do you agree with that? And use that as the stepping stone if you will for kind of the next iteration going forward.

DR. SHINE: That could be a key part of any planning process.

DR. HARLANDER: And I think you'd have to - I totally agree with you. I have personal concern about the pipeline of antibiotics and the implications of that in the broader sense to both human and animal health, and that isn't something that we you know delved into in this. But I think this could be a platform for a broader - and I guess I would advocate, even though we had trade associations that represented producers and processors, this is the kind of information that needs to get all the way down to the individual producers in the country. You know, we often focus on kind of that high-level professional societies, but we need a way to deliver this message so that the understanding is there all the way down to people who produce food, whether it's spinach, or animals, or you know whatever the food

safety issues are.

DR. CASSELL: I'd like to ask our colleagues at FDA if there's precedence for having this kind of public meeting that Lonnie was talking about, and maybe if it were held in collaboration with some professional organizations that could help fund such a meeting, like ASM for example. I think ASM I can almost guarantee would be very interested in helping to support this and I think it's a really good idea. When I look back a decade ago, or a little more I guess than that, when the topic of the use of quinolones in animals came up it was one of the best meetings in antimicrobial resistance issues that I think I've ever been to because I think it was the first time in history that the veterinary antimicrobial use committee had met with the human antimicrobial review committee. I'm not sure that that's the case, but I think I was told that. But Sue, the thing that was neat about it is you had individual producers there, in fact individual farmers that you know were concerned about this whole issue and the health and so forth. So it was, you had a big mix of people that knew a lot about the issue. So I think - this was right after, too, I think the

salmonella DT-104, so there was a lot of personal concerns, especially in Vermont and other states like that. But I think this could be a really good thing. I think it could be good for FDA to show that leadership by you know calling together a meeting as a result of this report and in order to get the resources we could get I think AVMA maybe. I can't speak for them, and CDC don't you think might be interested too?

DR. SHINE: Maybe Dr. Woodcock could comment with regard to that. Also Dr. Woodcock, as with all of these reviews we don't want to just put it out there. We would like to get a response. In this case it would involve multiple agencies, so whether this fall or early next spring and so forth it would be useful to be able to get the response to these critiques. If people want to push back because they think it's wrong, we ought to hear what they're interested in and so forth. And I understand - I'm not asking for a critique or anything else, but I understand there are a number of people in the audience associated with NARMS. David White, Steven Sundlof, Pat McDermott. After your comments if they want to make any observations or whatever I think the

Science Board would be interested in any comments they want to make.

DR. WOODCOCK: Thanks very much. I think we will definitely take all these recommendations very seriously and including the idea of having a meeting or public workshop or whatever. And we can definitely get back to the board as a response. We will definitely do that. I'd like to hear from Steve Sundlof and Doug Throckmorton and probably Bob Brackett and other people who were involved in this.

DR. SUNDLOF: There you go, thank you.

DR. SHINE: Do you want to just identify yourself?

DR. SUNDLOF: Yes, I'm Steve Sundlof, not Dan Schultz. I'm Director of the Center for Veterinary Medicine. And first of all, I would really like to express my appreciation to the subcommittee for a very, very thoughtful report. I've been involved in NARMS since its inception. You know, over the last 10 years I've been very much deeply involved with it on a day-to-day basis and yet when I read the report I found all the things I was hoping to find in the report, but I found things in the report that I wasn't expecting

and had never really considered before. And I think some of the suggestions were very creative and I need to look at it in a very different light, especially things like your sampling systems aren't robust enough to really give us a good representative example, but they could be used for other things and that was very enlightening to me.

We haven't had a chance at this point to discuss it internally, but over the next week or so we will have that opportunity and really try and get a sense of what we think is possible and doable. It'll also require us to coordinate with CDC and USDA to make sure that we're all thinking along the same lines. I certainly support the idea of having a national symposium on this issue. In addition, and I'm sure the subcommittee is aware, that on an international scale the Codex Alimentarius has now taken up this issue and they will be holding a workshop or ad hoc workforce this fall and it will go for the next four or five years in which all of these things, NARMS as a surveillance system, but all kinds of other measures that can be used in addition to these kinds of surveillance systems in order to mitigate

antimicrobial resistance as a result of the use of these antimicrobials in animal agriculture.

So just in summing up then, again I think the committee has done a great job on this. It will give us a lot of food for thought. I'm particularly happy that the committee reinforced my views that this is really a mission critical system for the FDA and I think for public health in general, and having the committee recognize that I think really helps us to try and move it to the next phase, so thank you.

DR. SHINE: Any other comments from any of the other folks associated with NARMS? Again, we understand that you have not had an opportunity to discuss it or whatever and we look forward to that kind of feedback. Please.

DR. THROCKMORTON: Yes, and I'm also not Steve Galson. I'm Doug Throckmorton. I'm Steve's deputy who should be here shortly. Like Steve Sundlof I'd like to thank the committee. I thought that was a terrifically thoughtful report. Coming from the Center for Drug Evaluation Research as Gail pointed out we're not the focus of this report appropriately, but we are very mindful of its potential implications as far as

the development of new antibiotics and would look forward to working with you in any way that it would be useful.

One thing that I was particularly struck with and we were actually talking here amongst ourselves a bit was the database. And like all good policy decisions, you know the next steps here start with good data. I don't know where to take that observation except to say I think that database is an issue that really resonates a lot of us around the table. Janet and I both being on be Bioinformatics Board and things, we see the challenges in putting those kinds of databases together and making them interoperable and accessible and secure and you know, those kinds of things, but it's a terribly important next step and I applaud you for raising that as a particular issue and especially that one. So thank you. We'd be happy to work in any way that we could to facilitate this and thank you very much.

DR. SHINE: Dr. Cassell? Okay.

DR. SASICH: Because of the critical nature of the report, would it be worthwhile or possible for the FDA to brief members of Congress

on the results of the report and spend some face to face time with them trying to explain it to them? I think it would be highly worthwhile. Another thing that just kind of struck me out of the blue in terms of the sampling, and I was trying to think of healthy individuals who might participate in such a surveillance program. What about new inductees into the armed services? Could you get the Department of Defense involved? And I think you'd want to wait until after they passed their physicals so you're sure that they're healthy.

The other thing about the availability of antibiotic utilization data or information. I guess I'm not quite clear, are you talking about use on the farm, numbers of prescriptions both in terms of what veterinarians are doing and what is done in the human clinic? We do have the prescription data and the FDA uses that. Now we see these in briefing documents all the time. It's confidential commercial information, or it's proprietary information. We're not supposed to release it so we can get the number of prescriptions for antibiotics. But I suppose you'd want to be able to see them at different

geographic areas which might be - and I think you could do that too because it is possible for market research firms to identify exactly how many and what drugs physicians write prescriptions for. And I think the agency pays for that data with the promise, if I'm not mistaken, with the promise that they'll keep it confidential. But I think this is an extremely valuable project.

DR. SHINE: Dr. Cassell and then we'll see if Lonnie wants to give a benediction.

DR. CASSELL: Okay. I was just going to ask Dr. Sundlof, given these international activities that you referred to is there any urgency in terms of trying to pull a meeting together in this country that might help inform some of those international policies that are being considered?

DR. SUNDLOF: I think - well, let me just say Gail that there are a number of things happening at the international level. Some of the things that we've done in terms of creating these critical lists of antimicrobials, the ones that we have the greatest concern about is now happening in WHO and the OIE, the animal World Health Organization. So that process is moving into the

international arena. That's one thing. The task force is a 5-year process so I think in terms of the urgency it's probably - we probably do have some time, but everybody I think in the codex process, the codex countries are really looking to the United States for guidance on this because we have put programs in place like NARMS and then coupled with the regulatory pathway for drug company sponsors to follow in getting their drugs approved. But I think as the subcommittee found out, there is a tremendous amount of interest from a tremendously diverse audience within the United States to move forward on this issue. And I think we've gotten good marks from the consumer advocacy groups and others for going as far as we have, but they want to see more and I think that as we work our way through the recommendations of the committee and that we involve our stakeholders in those discussions we can plot a course forward and that will help drive the international decisions that are going to be made.

DR. SHINE: Dr. King, any last words?

DR. CASSELL: I was just going to say, please correct me if I misrepresented my perceptions about WHO and what they're doing about

antimicrobial resistance.

DR. SUNDLOF: Yes, we're aware of the individuals. I agree there's no one single program called antimicrobial resistance, but we are constantly working with individuals within WHO who this - for which this is a major part of their job description.

DR. SHINE: Dr. Woodcock?

DR. WOODCOCK: It's just a very small process point from the standpoint of the subcommittee will give - has given this report to the Science Board which will then at some point actually transmit it to the FDA which perhaps you have, but that's how it works. And so we actually haven't formally received it until we receive it from the full board.

DR. SHINE: I'm about to make a statement in that regard.

DR. WOODCOCK: Excellent. Then in that case -

DR. SHINE: That was one of the reasons that I asked about audiences because we want to see the distribution relatively broad and that can take place through the FDA.

DR. WOODCOCK: Yes.

DR. SHINE: So far as the board is concerned, if Dr. King and Dr. Harlander have nothing further to add at this point, without objection I propose that the Scientific Advisory Board accept this report from its subcommittee, transmit it to the Commissioner of the FDA with a strong recommendation that, (a), it be disseminated widely and that we've made some suggestions with regard to potential audiences for it and we may have some additional ones. And secondly, that there be a response from the participants in the program within the next six to twelve months indicating their reaction to the report, the actions that they're going to take in response to the report, any concerns that they have about it so that we can learn whether we're making some progress in terms of the activity. Is there any objection to that course of action? Hearing none, it is transmitted.

DR. WOODCOCK: Thank you very much and you should hear from us before six months for sure.

DR. SHINE: I said "within." All right. We'll move on to hear from Dr. Cassell. I remind you that the Commissioner met with this

board a year ago and at that time charged us with a major project with regard to evaluating the relationship between science and the FDA and its regulatory function. Dr. Cassell, despite injury and a variety of other interruptions has done an absolutely spectacular job. I call your attention for those of you who have a copy of the agenda book, the roster of scientists that she has recruited to this effort which is indeed remarkable and which will be I believe Carlos shortly published?

DR. PENA: It's on the web already.

DR. SHINE: It's on the website. She has been working very diligently on the project and is going to give us a progress report as to where we are. Dr. Cassell.

DR. CASSELL: Thank you, Ken. I would just like to remind everybody that it is actually just a progress report on the process and kind of where we are in terms of our review. I would also like to say that we are slightly behind because of a little accident, but we are moving I think at a very good pace and a very thoughtful pace. I want to just make a few general comments before talking to you more about where we are actually in the

review.

First of all, Dr. Von Eschenbach this morning reminded us all that his vision and the vision of FDA is that it will not only be a science-based agency, but a science-led agency. I think that's a very important point because the charge to this subcommittee of the Science Board really is to look at science within the FDA, its current role and status as it affects the regulatory mission of the agency. And when we say "science," we not only mean research, but also literature, investigation and data-mining, et cetera. So it's in the general sense of science. I would say too that it is not a review of individual research programs, so don't get the idea that at the end of this review that you will have an assessment of each individual research program or aspect of science within the agency. That is really not the intent of the review. What I would say is that the areas that we have chosen to review actually we feel are extremely important, looking at where the agency is now and where everyone would like to see the agency in the future.

And so the other thing generally I'd

like to say about the review is that it's very data-driven. Just to have perceptions or to base recommendations on perceptions or anecdotal evidence I think doesn't do anyone any good, and so we are a very intense group I must say and a very data-driven group. And along with that I would hasten to add that the FDA put in place an internal committee that basically has been engaged in this review and helping to generate the data, or provide the data I should say to this review group. And I can't say enough about how much work the members of the FDA staff have gone to to provide that data in a very responsible and thoughtful way, and we have asked for a ton of data and are in the process of reviewing it.

And I would just say that also, and again general terms, I wanted to just mention a few things about this committee. First of all, the committee is a subcommittee of the board, and just has Janet has just pointed out to you about the NARMS review, the results of this review will be actually presented to the Science Board and then we will value very much and depend on this committee really to report back and review to the subcommittee in terms of your thoughts and

questions and challenges. It may be that we'll have to go back and get additional data depending on what this board actually says. And members of our committee contain members of this subcommittee. Allen Roses and Barbara McNeil who's not here are members, as well as myself. Dr. Shine has been an active participant also of this committee and I must say extremely supportive.

So I just also want to make one other point and that is that at the very outset no one wanted to be a member of this review committee if in fact it was going to result in a report that was going to sit on a shelf and not make a difference. Because it's very time-consuming on behalf of the agency and certainly on the part of the review committee, so we were absolutely adamant about that and almost every time we've seen Janet or seen Dr. Von Eschenbach, we re-ask the question can we be certain that this report will make a difference. And every time without a minute's hesitation we've been assured that in fact it will make a difference, it will be considered very thoughtfully. It cannot be guaranteed that all of our recommendations would

be implemented, but in fact that's what you would hope would happen, right? No group is that wise.

I wanted just to also point out a few things about this subcommittee and this review that make it in my opinion unique and one of the reasons I think it's very important. One is the timing of the committee review. As you know the agency this fall celebrated its hundredth anniversary and in that hundred years it's been less than four times - in fact, I think this may only be the third review, correct me if I'm wrong somebody at FDA, that - I know it's been here a hundred years, but I think this may only be the third time that any external committee has reviewed the agency as an intact body and looking at all the parts and how it functions together to accomplish its overall mission. To me that's extremely important because many programs have undergone intense review, even in the course of our subcommittee's review, but that's a very different thing than looking, trying to look at the entire agency and get a feel for how it works together, what are the crosscutting issues, what are the recurring themes especially as it relates to research within the agency, science within the

agency, how the priorities are established in each of the centers, what is the - and research talent base within those centers and programs, and then what about the gaps as we look towards the future in terms of what we anticipate will be coming in the way of new products, new devices, new vaccines based on current research and science.

So realizing again that this is a unique committee in terms of the fact that it's looking at the agency as a whole, there's another very unique aspect and that is that if you look at most of the review committees, like especially the recent IOM review report on drug safety that was issued in the fall and you look at the membership of that committee and because for obvious reasons there were no members from the industry on that committee, or really people that were close to either the agency or to companies that were members of that committee. And I think that was essential that it be that way for obvious reasons. But in fact most of the reviews in the past, even the Corn report which is a recent - one of the three reports that looked at the entire agency, as well as the other one, the Edwards Commission, if you look at it, it didn't have this combination of

industry expertise and academic expertise and by the way, government expertise on the committee. So we intentionally brought together the three sectors to try to get the best mix of people that would have familiarity with the agency, with its mission and also that are very research-intensive with respect to both industry and the academic sector so that we could do a better job of assessing what the future might look like in terms of anticipating what the future challenges will be for the agency, both from a public health standpoint, but in particular also from the product review standpoint.

So you have a list of the members of the committee and so I won't belabor the point, but to say that each one was really chosen very carefully. And I'll just point out a few to give you some idea of the breadth and the depth to try to match the breadth and the depth of the agency and the complexity of the agency. But just for example, looking at the issue of genomics and what that may entail for the future we have David Altshuler who is at the Broad Institute and actually the founder of the program in Medical and Population Genetics. Tom Caskey, who has had a

distinguished career in the academic world, but also was at Merck and headed up their genomics program for a period of time. He's a member of both the Institute of Medicine and the National Academy of Sciences. In addition, we have Bob Goldstein who's the Scientific Director of the Juvenile Diabetes Foundation who spent a lot of time thinking about genomics issues and research as it relates to juvenile diabetes. In addition, we have in that same group that is looking at a lot of issues that relate to genomics is Lee Hood, the inventor really of a lot of the technology we use today for sequencing the human genome and microbial genomes and the technology for integrating this data into systems biology. He is currently the President of the Institute for Systems Biology and has been a very active member of the committee so far.

With regard to how we have also chosen others for specific reasons, Cathy Woteki is a member of the committee. She is a former Deputy Secretary of Agriculture, but in addition is now with the Morris Foundation. She went to the Morris Foundation from being the dean of the veterinary school at the University of Iowa. So a

lot of depth there in various aspects. We have Eve Slater who is a former Assistant Secretary of Health, but was also in charge of regulatory for Merck for years in the area of vaccines, but now is the Senior Vice President for Policy worldwide for Pfizer. So she comes with a variety of background experiences. We have Roy Vagelos, a former CEO of Merck. We have Phil Needleman, again someone with a lot of academic experience, but also industry experience. We have Dale Nordenberg that I referred to who is at the CDC and very intimately involved with their information technology and database management, particularly as it relates to flu preparedness now, but has been very active in terms of the Secretary's committee on information technology issues within the different agencies. Sang Kim is leading the IT group. Sang is a former Chief Information Officer for Pharmacia for Lilly. He's a member of the National Academy of Engineering and took a year's sabbatical from his endowed professorship at Purdue to oversee the National Science Foundation's IT program. So he comes with a fairly unique perspective I think of information technology as it applies to the pharmaceutical

industry and to a federal agency. The only other thing I would say is that we also have Al Gilman. Al is a noted pharmacologist. He also happens to be a Nobel laureate.

And the thing that's so exciting about this group is everybody is engaged. Some of the groups have weekly conference calls and they are very, as Steve can tell you, pretty intense. And so we have divided the group into those main areas within FDA looking at the different centers, CDER, CBER, CDRH, CVM, CFSAN, CTR, and then three groups that we consider crosscutting, looking specifically at genomics, information technology, surveillance and biostatistics. Some of the individuals serving in these capacities have been former FDA employees that know again the agency, but are now in the academic world and see it from a different perspective. That's Susan Ellenberg, purposely chosen because she was also a member of the IOM Drug Safety Report so already had a lot of familiarity with what the issues were.

So enough said about the committee. I would say that each of those committees as sub-working groups is at a different stage right now in terms of their data-gathering and data

analysis. The intent, however, is to have an early draft to the Commissioner by early fall, and in the interim would also be interviewing major stakeholders, some of the trade associations, but also some thought leaders, former Secretaries of Health, former FDA Commissioners to get their input, and then lastly to ultimately have public input on this report. And I would ask Ken or Allen if they would like to add anything to what I've said, and then also maybe Janet, you or Carlos would like to add. I'd like to recognize Carlos in particular. All of the FDA staff have played a tremendous role in terms of helping us with this effort, but Carlos I think works 24 hours a day, 7 days a week and I appreciate it, Carlos. I know everybody else does as well.

DR. SHINE: Allen, do you want to make any additional comments?

DR. ROSES: Well, just I think the only thing that I would add is that being on one of the subcommittees that has weekly or sometimes biweekly conferences the heterogeneity of the subcommittee is very, very important. It also brings some challenges in that there's some necessary time that it has been taking to put the

expertise together so that we can actually become mission critical. And I think that's happened and I think the type of development that's occurring now will be at a fairly rapid rate.

DR. SHINE: Before I ask Janet to comment, Norris, would you just comment on the schedule with regard to our fall meeting, public meeting, and the plan to try to complete the report in December?

DR. ALDERSON: I think the plan right now is that we will have the board meeting in October, will be a presentation of the draft report to the board at that time. And from then to December will be an opportunity for public input into that document with a final presentation of the report to the board in December.

DR. SHINE: But the point is that we will be going public with a draft of the report at the October meeting.

DR. ALDERSON: That's correct.

DR. SHINE: And we would -

DR. ALDERSON: Actually, the plan is -

DR. SHINE: I'm sorry.

DR. ALDERSON: - late summer make a draft report available -

DR. SHINE: Publicly, right. But - correct. As far as the board is concerned it will receive that draft at its October meeting.

DR. ALDERSON: That's correct.

DR. SHINE: I'm hoping that we will have some opportunity for some public comment even at that point as part of that meeting, and then there will be an opportunity for the subcommittee to make changes and so forth on the basis of the public meetings, on the basis of the board's work, with the idea that we're shooting for a December endorsement to the report. I would also reiterate the observation that Dr. Cassell made that we are going to be thinking very hard with the agency about how and in what way we disseminate that report. And you know, some of you know that I spent 10 years at the Institute of Medicine and if there was one thing I learned from that experience it was that the dissemination plan was in fact often the most important part of what you did because you could always get very good people, smart people to say smart things, but unless you could disseminate it in an appropriate way it was just more smart things being said. Dr. Woodcock?

DR. WOODCOCK: Well, so far we really

appreciate both the quality and the depth and breadth of the subcommittee that has been formed. We've really enjoyed the interactions with all the groups. Well, we recognize, you know we've given forth quite a bit of data and information to all these folks, so we recognize what a challenge it is to integrate all this. But we need to develop, as we've discussed before, a vision for FDA research and science for the future. Where are we going with this and what are - you know, what are the highest priorities and so forth. And I think as we've heard all day today we can see the need for research and the need for our access to all sorts of scientific expertise because we never know the kinds of problems that are going to pop up to the crisis level at any given time. And we need to be able to respond to protect the health of the people in this country and the animals in this country as well. So we really look forward to this.

And what we had hoped to do, Dr. Shine, in order to - you know for the dissemination and so forth to start in the late summer/early fall, we would operate a docket for the committee and then we would provide you with the comments, the

public comments that had been submitted to the report and you know organize those for the committee so that when you have your October meeting you know what has been said and you'll have an opportunity there for public comment on the report as well because it will have been out there for awhile and people could have absorbed it. And then we can finalize the report and we will need to talk about - we internally, what our action plan is which I'm sure we will take back to this board, all right, for input, once we develop an action plan from the report, but also the dissemination of the report to all the other involved parties or stakeholders.

DR. SHINE: Other comments, questions? Dr. Harlander.

DR. HARLANDER: I am very impressed with the roster of folks that you've been able to attract. The one thing I'm concerned about is I don't see any food industry representation on the committee and I would just - I know that it's a crosscutting scientific issues that you're dealing with, but I think that the food sector would come at that science in quite a different way than what the pharmaceutical or drug side would. And so

when that draft report is available, I think it really is very critical to get that out because it is the Food and Drug Administration and I just want to make sure that the food part is you know well - that we get a lot of input from that side as well.

DR. SHINE: Dr. Cassell?

DR. CASSELL: Very good point, Sue. I would say that Cathy and Jim and John have made an effort to talk with the stakeholders in the food industry fairly extensively. I can't remember the list right off the top of my head, but they certainly I think have reached out and will continue to be doing those interviews if you will over the next six weeks. But you make a good point.

DR. SHINE: Other comments, suggestions? Observations? We're - poor Dr. Woodcock was under time pressure this morning and all of a sudden we're running ahead. Is there anyone in the audience who would like to make comment during the public session? Any public comment from anyone with regard to - this is with regard to anything today, or anything that they want to talk about. These open sessions are not

restricted to a particular report. Hearing none, the - I don't think I'll read the statement.

Well, let me make some closing comments, and again I'm embarrassed Janet. We could have - given the importance of what you had to say, we - but we will be revisiting IT I think in a big way. First of all, I want to again thank the committee that reviewed NARMS. I believe that the sense that - and two of you have now used the phrase "mission critical" so it's echoing back and forth I think here that this is an extremely important action. And I'm very pleased with the quality of the report, the reaction to the report and I think Gail's notion that this offers the opportunity for a major convening activity for stakeholders is a very important recommendation that I hope we will be able to follow up with.

I think so far as the Science Board is concerned, the science review, the next four or five months are going to be very intense. The committees are working very hard, the staff is working very hard. I again want to thank Carlos and Norris not only for supporting this Science Board, but also supporting the science review effort which has not been an uncomplicated one and

I'm hoping that that review will throw a good deal of light and that we will have a dissemination plan for it that will make a lot of difference.

As I indicated in my comments to the Commissioner this morning, I think the Science Board continues to be very concerned about programs in safety, both of food and drugs as you've heard today, and the process by which we assure safety, the relationship between the approval process and post-approval surveillance, the use of IT to enhance that and I think this is a subject that is going to continue to echo. One of the issues that the science subcommittee has been debating is what are the themes around which it will make its scientific recommendations, and it is very clear that food and drug and biologic safety, device safety may be one of the most important contemporary messages about why and when it is critical to have good science and good research available to the FDA.

I consider this to be a very important transitional meeting in the history of the Science Advisory Committee, the Science Board, because it started a number of years ago primarily as an activity in which some of the advances in programs

of the FDA could be highlighted, and although there were good interactions at those meetings, often the committee met twice a year and had a reunion and then met again twice a year. I think this is a very important transitional meeting because it reflects some really important changes in the role of the board. The charge from the Commissioner to review the science programs is an extremely important one. I think one of the things that's going to come out of that report will be the requirement or the necessity for in fact even more comprehensive reviews of the science and the research in the agency over time, and particularly the use of extramural reviews. Some parts of the FDA do that very well, others do not and I believe the Science Board is likely to be charged with an oversight of that process. And the NARMS review that we've just heard is a good example of that process as I believe it working well.

I'm also very pleased that in the course of the melamine situation the Science Board was able to play a useful role in identifying peer reviewers. We still have some logistical difficulties in that the ad hoc creation of a

subcommittee to review something raises FACA issues and so that's the reason you end up with comments from six peer reviewers peer reviewing independently.

Somehow it seems to me over time we need to evolve mechanisms by which we can do very timely intense kinds of reviews about important issues confronting the agency in a manner that when necessary can involve, whether it's a conference call or face to face meetings, but would allow the benefit of the resources the board can bring to bear to produce the best possible advice in the shortest possible time, recognizing that that's got to be done within the confines of the legal structure. So that I think that the evidence that the board was in the position t do this, the evidence that the board is continuing under Gail's leadership with a long, much longer range project and so forth is an extremely important development and I hope that we will continue to be called upon when necessary to do what the agency needs to approve its performance, its integrity and the quality of its work.

Are there any other items that anyone from the Science Board wants to bring to the

table? Anything Dr. Woodcock that you want to raise at this point? Hearing none, the meeting is adjourned.

(Whereupon, the foregoing matter went off the record at 2:19 p.m.)