DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

SCIENCE BOARD MEETING

8:08 a.m.

Friday, October 25, 2002

5630 Fishers Lane
Room 1066
Rockville, Maryland

P A R T I C I P A N T S

FDA Science Board

Robert Langer, Sc.D., Chair
Susan M. Bond, Executive Secretary

Martin Rosenberg, Ph.D.
Michael Patrick Doyle, Ph.D.
Robert Nerem, Ph.D.
Harold Davis, D.V.M., Ph.D.
Jim Riviere, D.V.M., Ph.D.
Josephine Grima, Ph.D.

Lester Crawford, D.V.M., Ph.D., FDA
Norris E. Alderson, Ph.D., FDA

Presenters

Joseph Levitt, Esq.
Andrea Meyerhoff, M.D.
Margaret Miller, Ph.D.
Philip Noguchi, M.D.
Kathleen Uhl, M.D.
Susan Wood, Ph.D.
Janet Woodcock, M.D.
Kathryn Zoon, Ph.D.

Also Present:

Daniel Casciano, Ph.D.
David Feigal, M.D.
Steven Galson, M.D.
John Marzilli
Betsy Natz
Bernard Schwetz, D.V.M., Ph.D.
Stephen Sundlof, D.V.M., Ph.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

DR. LANGER: Good morning. My name is Bob Langer. We'll just call the meeting to order. I just want to make one announcement and then have people go around and introduce themselves.

The announcement is, if you looked at the original schedule that was posted, there's going to be one change. Dr. Lumpkin can't be here today. So the schedule will be--there's a new handout that people hopefully have, so there will probably be a little bit earlier break for lunch so people can eat more.

So, with that, why don't we start and we'll just go around and introduce ourselves.

DR. RIVIERE: Jim Riviere, North Carolina State University.

DR. LANGER: And you're a member of the Science Board.

DR. RIVIERE: Member of the Science Board.

DR. GRIMA: Josephine Grima. I'm the consumer representative for the Science Board. I am now with the National Marfan Foundation.

DR. NEREM: This is Bob Nerem. I'm from Georgia Tech, a member of the Science Board.

DR. DAVIS: Harold Davis from Amgen, member of the Science Board.

DR. ROSENBERG: Marty Rosenberg. I'm also a member of the Science Board, and I'm on sabbatical, teaching at the University of Wisconsin.

DR. DOYLE: I'm Mike Doyle with the University of Georgia, and I'm also a member of the Science Board.

DR. SCHWETZ: Bernard Schwetz, Senior Advisor for Science at the FDA.

DR. LANGER: I'm Bob Langer, Science Board. I'm from MIT.

DR. ALDERSON: I'm Norris Alderson, Senior Associate Commissioner for Science at FDA.

MS. BOND: Susan Bond, Executive Secretary to the Board.

MR. MARZILLI: I'm John Marzilli. I'm with the Office of Regulatory Affairs.

MR. LEVITT: I'm Joe Levitt, Center for Food Safety and Applied Nutrition, FDA.

DR. ZOON: Kathy Zoon, Director of Center for Biologics.

DR. CASCIANO: Dan Casciano, National Center for Toxicologic Research.

DR. SUNDLOF: Stephen Sundlof, Director of the Center for Veterinary Medicine.

DR. GALSON: Steve Galson. I'm the Deputy Director of the Center for Drug Evaluation and Research.

MS. NATZ: Betsy Natz. I'm with the Office of External Affairs.

DR. LANGER: Thank you all. I did want to make one other announcement. Kathy Zoon, who introduced herself a minute ago, was elected two weeks ago to the Institute of Medicine of the National Academy of Science.

[Applause.]

DR. LANGER: Anyhow, with that, let's turn it to Dr. Crawford for introductory comments.

DR. CRAWFORD: Thank you, Dr. Langer.

We have four members of the Science Board that have served long, well, hard, and painfully who will be retiring from the Board. All of them have to be recognized, and must be, starting with Owen Fennema, Ed Scolnick; Rita Colwell actually has called from Stockholm. We can only imagine what she's doing in Stockholm. She may be trying to one-up Dr. Zoon.

[Laughter.]

And, finally, the long-suffering but brilliant Chairman of the Science Board, Dr. Bob Langer, and all of you who are devotees of Time Magazine may recall on August 20, 2001, that our man Langer was featured. And there is a very large picture of him, which I'm going to embarrass him with, and it does not show a defective ocular situation. It shows him looking for the optimal drug delivery system, and it indicates some essentials

which I am going to embarrass him with. You may not leave the room. It says he was born August 29, 1948, in Albany, New York. What got him started was a Gilbert chemistry set, which he received when he was 11 years old, that he still has and plays with most evenings. [Laughter.]

The turning point in his life was a post-doctoral fellowship with cancer researcher Judah Folkman, which took him off the chemical-engineering career track. And his modus operandi, he looks at problems upside down and inside out. And that's why he's so comfortable working with FDA.

So I have the honor of presenting the award, which I hope you will enjoy and hope you will open now. At the University of Georgia where I worked for about 20 years, we got a Gruen watch. This is a Gruen watch. This is a big one.

[Applause.]

DR. LANGER: Thank you very much.

DR. CRAWFORD: Take a moment.

DR. LANGER: It's not going to blow up, I hope.

DR. CRAWFORD: No, no.

DR. LANGER: It does look a little something like a watch. Well, thank you very much.

DR. CRAWFORD: Well done.

[Applause.]

DR. CRAWFORD: Now, at this point I would also like to announce the new Chair for the Science Board beginning with the term of January 1st of next year, and it will last longer than that, depending on his performance, Dr. Michael Doyle of the University of Georgia. Mike?

[Applause.]

DR. CRAWFORD: All of us are a bit--we have a couple of changes to the program. First, Dr. Mark McClellan is unable to be here. As some of you know, he is still doing his White House duties as one of the three members of the Economic Council that advises the President on the nation's economy. Dr. McClellan will be sworn in probably on November 8th and will show up here, we all hope, and especially me, within a few minutes after that. His replacement at the White House--actually, that is his starting date, so we believe that things will happen at that point. He's already been confirmed by the Senate and, therefore, is called Commissioner Designate until President Bush swears him in.

Let it be said for the record that Dr. McClellan, if he does make it by November 8th, will be the youngest FDA Commissioner ever at the age of 39-plus, but 40-less. But if it goes as late as November 12th, David Kessler will still maintain that honor.

[Laughter.]

DR. CRAWFORD: So we're working with POTUS to get him sworn in before then because that is a notable distinction, and Dr. McClellan has begun his process of getting oriented to FDA, and we are all very, very impressed.

He has been our primary White House liaison during the time that I've been here, which is now eight months, and he will be very familiar with all of FDA's matters. Anyhow, I think it is going to be a little bit dangerous to orient him, and I'm trying not to be involved in that process because he's already oriented, I can assure you of that.

Now, one other thing we want to mention, and that is that Dr. Lumpkin is with Dr. McClellan and, therefore, both of them are unable to be here. If that makes sense to you, then I'd like to speak to you after this meeting. But big things are happening, so we had to take off--we had to change the program both to reflect Dr. McClellan's inability to make opening remarks and also for Mack's inability to talk about the CBER/CDER switch.

Dr. Lumpkin has been Chairman of the Implementation Team that has put that into place. I now have before me the recommended approach. This has been

shared with CBER, and we are now in the process of discussing with them the fine-tuning of that.

Last night at the dinner, I discussed some aspects of that, and also the idea that there would be some other organizational considerations, and the Science Board, at least one of you and hopefully two or three, have agreed to form a subcommittee to look at future changes, and we may need a permanent subcommittee, Mr. Chairman and Mr. New Chairman. So we'll be looking forward to working with you on that. And this kind of input would be very useful to us for future changes.

So, with that, I will turn the meeting back over to Norris Alderson to make other comments, and I look forward to being with you until the lunch, where I have to also go to the White House. And I have not been told what it's about, so that's life.

DR. ALDERSON: Thank you, Dr. Crawford.

I would like to second Dr. Crawford's comments regarding Dr. Langer. It's been a real pleasure for me to work with Bob since I've been in this position, and I really appreciate, Bob, the guidance you've given us over that period.

As Les mentioned, we are in the process of getting four new Board members beginning in January. They've been selected. They're going through the clearance process, and as soon as they've made the

clearance, we will be making an announcement of those individuals.

I do want to point out that the FDA Science Forum for 2003 has been scheduled. There are copies of the announcement outside on the table. It's scheduled for April 24th and 25th at the Washington Convention Center. We encourage Board members to attend that if they can.

This is one of the premier science activities of FDA. It's becoming of more significance in the science arena for FDA than ever before. Last year we had over 1,200 registered for it.

This year's theme will have three areas: one, risk management; second, novel science initiatives at FDA; and, third, public health initiatives post-9/11. So we think we've got an outstanding program planned with outstanding speakers, and we certainly encourage everyone to attend.

As a note of follow-up items to the April meeting, you'll remember we had considerable discussion regarding the development, or lack thereof, of antibiotics that is going on in the industry. Dr. Crawford is pursuing with us the additional time at the April meeting of this Board to pursue that further, and I'll be talking with many of you in the next few months about your view on how we need to address that as a

program for the Science Board. But I just want to alert you to that.

That's all I have, and I think Sue has some administrative requirements she needs to tell everyone about.

MS. BOND: I have to make comments for the public record, if you'll bear with me here.

The following announcement addresses the conflict of interest with respect to this meeting and is made part of the record to preclude the appearance of such at the meeting. The Food and Drug Administration has prepared general matter waivers for Drs. Nerem, Davis, Grima, Riviere, Langer, Rosenberg, and Doyle. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office in the Parklawn Building, Room 12A30. The waivers permit them to participate in today's discussion of counterterrorism initiatives, the new CBER Office of Cellular, Tissue, and Gene Therapies, Pregnancy Labeling Study issues, and the agency's Pharmaceutical Manufacturing Initiative.

The topics of today's meeting are of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. The participating committee

members have been screened for their financial interests as they apply to these general topics. Because the topics impact so many institutions, it is not prudent or practical to list all of them at this time.

We acknowledge there may be potential conflicts of interest where, because of the general nature of the discussion before the committee, these potential interests are mitigated.

Now, to the important other housekeeping things, just for the public we invite everybody to have coffee and Danish up in front of the room here. There are phones outside behind the guard station. The rest rooms are right outside the door. We'll be breaking for lunch--well, Bob will call the lunch. We may be breaking a little bit early. And there's a list of restaurants outside on the table for those of you that want to go somewhere.

Public comment will start at 1 o'clock, and remember to push the microphones on when you talk. And that's all.

DR. LANGER: Thank you very much.

So now I guess we're ready to start, and the first discussion will be counterterrorism initiatives at the FDA, and Andrea Meyerhoff is going to lead that.

DR. MEYERHOFF: Good morning. Thank you very much for asking me here today. Can you hear me?

[Pause.]

DR. MEYERHOFF: Thanks. Good morning. I'll say again thank you very much for asking me here today. What I'd like to do is provide something of an overview of our counterterrorism programs and then--it went off and on here. I'll stay away from the microphone--and then present something of a sampling of scientific issues that have arisen in this area for the consideration of the Science Board.

The way I'd like to proceed is to make some very general comments about our mandate in counterterrorism or what does FDA do in this area. I'd like to go over our strategic plan, which has been updated and made comprehensive in the past year. I'll talk briefly about how we're organized across the agency, and then proceed to talk about the scientific issues that I've selected for discussion this morning.

If we take a step back and look at the sort of big picture of the agency, I think we can see FDA responsibilities in counterterrorism in the context of our dual identity in both public health and law enforcement.

On the law enforcement side of things in counterterrorism, FDA seeks to basically assure the safety and security of our regulated products. And this is the whole range of products we regulate: 80 percent

of the nation's food, animal feed, the blood supply, radiation-emitting instruments, and the wide range of medical products that are used in this country--drugs, vaccines, and devices--as well as other biologics, I should mention.

On the public health side, we are looking specifically at our role to facilitate the availability of safe and effective medical countermeasures across the three risk areas in counterterrorism, and that is, to respond to the care of individuals who have been exposed to biological, chemical, or nuclear agents.

FDA regulations apply across the board to both the civilian and military populations, and I think when we think globally about these two groups in our country, there are some generalizations we might be able to make when we look at the public health needs of these two groups.

As I put this slide together over the last few weeks, I really had to question some of these statements. I would say these are general trends, and I'm sure we can find exceptions in both of these areas. By and large, civilians carrying out the activities of everyday living operate in areas of lower risk than do active-duty military. The civilian population includes special groups--children, the elderly, pregnant women--who may represent special medical needs.

Public health actions in counterterrorism are most likely to follow a sentinel event, such as a disease outbreak, as we saw last fall with the occurrence of the anthrax outbreak in this country. Again, I don't think a hard and fast rule, but something to keep in mind when we look at the needs of the military population, and that is, they have the potential to operate in the areas of highest risk--deployment to theaters of operation where there may be knowledge of or high risk for exposure to weapons of mass destruction. The population medically tends to be more homogeneous. These are generally healthy young adults. And in certain instances, the need for public health actions may really precede any sentinel event, but be more preventive measures.

Let me turn now and talk a little bit about just what the program areas are in counterterrorism. What are we doing?

One way to look at this is to contrast the agency's level of involvement and breadth of programs before the 11th of September last year compared to after that date.

These side-by-side bulleted lists give a sense of the changes that took place at that time. Before the 11th of September, our budget for counterterrorism was somewhere on the order of $8 million. The activities were largely focused on the availability of medical

products for biological events, that is, an adequate supply of drugs, vaccines, and biologicals; and much of the activity was focused in the Centers for Drugs and Biologics.

In the wake of the attacks of September 11th, the anthrax outbreak in this country, and the deployment of military forces to Central Asia, the agency really took a very broad look at all of the different activities that needed to come under counterterrorism and how those were going to be organized.

Our budget grew substantially. In 2002, that was somewhat in excess of $159 million. Counterterrorism became the new name of what we were doing. It was recognized, I think, about the 12th or 13th of September that we needed to drop the bio and understand that there were many categories of threat agents out there beyond the biological. And it encompassed now the full range of products regulated by FDA and certainly necessitated total agency involvement.

It was during this period that the agency's Strategic Plan in Counterterrorism, as it came to be named, underwent a substantial review and was an attempt to bring in this total agency involvement. And these are the four general areas that encompass what came under the rubric of counterterrorism, and it still does.

Goal Area 1 is the safety and security of our regulated products. It also gets referred to by the traditional law enforcement activities that are encompassed by that: deterrence, detection, investigation, and interdiction--happily referred to usually as DDII.

Goal Area 2 is the availability of safe and effective medical countermeasures.

Goal Area 3 refers to the agency's activities in emergency preparedness and response.

And Goal 4 really was set off by itself more because it has elements of each of the three preceding goals, and that is radiation safety.

I'm now going to talk a little bit about each of these goal areas to show how we have set various strategies within them.

The safety and security of FDA-regulated products may be looked at from three different angles: how we regulate imported products, how we assure their safety in domestic commerce, and how we integrate our information systems to assimilate this very large body of data that we collect on the vast array of products we regulate.

A very large component of these efforts is our food safety and security programs, and I think because

I'm going to be followed by Mr. Levitt, I am going to defer to him to talk more extensively about that subject.

The medical countermeasures area I think we can look at in three very broad strategies in which FDA gets involved. The first of these is research and development. As an agency, we provide substantial regulatory guidance to those sponsors of products, be they drugs, biologics, or devices, that are seeking an indication for a counterterrorism-related need.

Secondly, we have a substantial role in assisting in the stockpile and inventory of these products. This was illustrated very graphically to us during the anthrax outbreak last year. We were in very close communication with the manufacturers of the various drugs that were being given out as post-exposure prophylaxis--ciprofloxacin, doxycycline, and some of the penicillin products--in order to assure that there were adequate supplies, that manufacturing was understood, the available quantities in inventory were known to us and communicated to the various other parts of the government that needed to know that.

Lastly, in the medical countermeasures area is the issue of deployment. When a number of our regulated products would be used in this setting, there can be the need to collect data on how they were used and what the

outcomes were regarding both safety and efficacy in the patients who received them.

Some of the regulatory mechanisms that make these products available, such as the accelerated approval regs, the new animal efficacy rule, or the investigational new drug regulations, warrant that outcomes data be collected, and much of our planning in counterterrorism looks at how we will go about doing that in what is likely to be a large-scale and rapidly evolving public health emergency.

Emergency preparedness and response encompasses a broad array of activities here in the agency, including our crisis management, what we do in emergency operations and exercising to prepare for terrorist events; our security programs for our personnel, our buildings, our documents, our communications; and I think that's the bulk of those categories. I'm just trying to think if I've left anything out.

No, I think that's pretty much it for that.

Lastly, I'll move on to radiation safety, which, as I mentioned earlier, encompasses the three areas I've already described. We have responsibility for the safety of radiation-emitting instruments of all kinds, and this again was illustrated to us when FDA got involved in discussions of what was a safe and effective way to

irradiate the mail that had been potentially contaminated by anthrax spores last fall and winter.

We participated in the discussions of what would be appropriate doses of radiation to use in order to accomplish the task at hand and at the same time not overexpose the operators of the equipment to excessive radiation.

There's a broad array of medical countermeasures that are needed in the event of a radiological or nuclear attack. A number of those are under development, and those developers or sponsors receive substantial regulatory guidance from the agency in manufacturing issues, safety and effectiveness, much as any other product does.

Lastly, FDA has certain responsibilities in emergency response in a radiation event, and those two are subsumed under the Counterterrorism Strategic Plan.

The breadth of our counterterrorism activities is clearly handled across the agency, and our office is responsible for coordinating those and serving as a point of contact for those outside of the agency who have any kind of counterterrorism-related inquiry.

We are in the process of beginning to form our Office of Crisis Management. I mention it here simply to point out the three functional areas that are coming together to work, and that is our Office of Security

Operations, Policy and Planning, our Office of Emergency Operations, and Counterterrorism.

I thought perhaps one way to illustrate how we assemble ourselves in counterterrorism is to take a look from first the outside and then the inside. Counterterrorism-related queries that come to the agency can come from a very, very broad array of sources. Certainly industry, academic investigators, foreign governments, our own government agencies, state and local governments, and the occasional concerned private citizen may bring to our attention issues relating to product development, new ideas in technology, issues regarding the security of our regulated products, and any of those are appropriate to bring to our office.

Some of the more common questions we handle are whether or not FDA is truly involved--is this a matter of FDA jurisdiction or does it belong to another agency?--whether or not we are funding any of these initiatives or can we assist people in finding where they might do that; and then if the product does belong in FDA, we serve as a guide to assisting in it getting placed in its appropriate regulatory home.

Inside the agency, counterterrorism operates through a steering committee. There are any number of points of contact across the agency that are part of this steering committee. The five product centers, the Office

of Regulatory Affairs, and the National Center for Toxicological Research all have ongoing scientific presences on the steering committee. In addition, there are a number of other functions across the agency that are needed and also serve on our steering committee.

As I put together my remarks for this morning, I tried to choose a sampling of scientific issues that I thought illustrated both the breadth of what is going on and also a common theme, and that is, the need for us to develop standards in a new arena, building on regulatory precedent as a guide. And I think one of the messages that is repeatedly driven home to me when we think about the risks posed by terrorist activities is they introduce the element of the unknown. They introduce agents to which we do not have a lot of experience responding, and they introduce new needs for regulatory action for which we may not have a lot of precedent. And I'll describe a few of those now to try and illustrate this. I'd like to look at certain questions in the area of medical countermeasures, in food security, and in radiation safety.

This is a list that has been making its way around a lot recently. It is the Category A list of biological agents. It was compiled in 1999 and published by the CDC. It represents the efforts of a number of government agencies looking at biological agents that are

capable of causing serious disease or death, and for which there seems to be some information that there is capability somewhere out there for someone to use them.

The diseases they cause--smallpox, anthrax, plague, botulism, tularemia, and hemorrhagic fevers--have very much been in the news, I think, some represented more than others. But one of the things I take home from looking at a list like this is that these are rather exotic agents when we think about disease. These are not commonly encountered agents in human disease. I think a couple of them may be more common in animal disease. But, nonetheless, up until the relatively recent past, we were not really thinking about what we had in our medical countermeasure armamentarium to deal with them.

So when we think about the development of drugs and biologics, one of the first things we recognize is that we're looking at the need to understand efficacy and safety of products that will have indications for which there is very little regulatory precedent. Up until last year, there had been a total of, I think, 18 cases of inhalational anthrax in this country. We still have had experience now with less than 30. That is a substantial paucity when we think about the kinds of information we need when we want to understand how a product works.

Similarly, the last case of smallpox in this country was in 1947. The antibiotic era was just getting

started then. The antiviral era had not even begun. These are diseases with which we have very little regulatory precedent for development of products.

The understanding that these are rare diseases, and certainly unethical to introduce into human populations for the purpose of study, turns us to the use of animal models to better understand the products that do need to be developed. And one of the biggest questions that we are wrestling with now, both in drugs and biologics, is what are appropriate endpoints, what are appropriate animal models in which to develop these endpoints to understand how these products work.

These types of experiments raise fairly quickly two other fairly important issues. One of them is the availability of non-human primates for the conduct of these studies. While a primate model is not required by the animal efficacy rule or for the study of product efficacy, primates are often the most appropriate animal to use, and certain species of them are in limited supply and warrant that we think strategically about how to use those resources in order to get the most information and the most useful products.

Similarly, the laboratory space that's available to conduct these experiments needs to be a fairly specialized environment with certain safety features and certain laboratory expertise among its personnel that is

not really widely distributed. And, again, building this up and understanding how we bring together laboratory facilities, experimental animal availability, and then getting the right models to do this in are substantial tasks.

I'm actually going to skip over this particular example in the interest of time and, rather, move on to a discussion of some of the issues about the development of diagnostic devices. I think I've made the point repeatedly now that we are looking at a new range of biological agents to assay.

If we take a step back and look at the evolution of the outbreak of disease caused by the intentional use of a biological agent, one of the things we will readily recognize is making an accurate diagnosis is a very, very important step and a very early step in the evolution of the outbreak. There are clearly public health and infrastructure and economic consequences linked to the information we would get from the diagnosis of such a disease and, therefore, putting an especially bright light on the need for good diagnostic tools.

As we look at our needs in this area, we need to ask ourselves: What is an appropriate level of sensitivity and specificity for these tests? How often can we be wrong at the expense of being right?

There's a need to validate these assays, make sure that they're reproducible. And in many ways, the parallels between good diagnosis and good prevention and treatment show us that there is a substantial amount of work to be done in both of these areas of the development of medical countermeasures.

I'd like to touch on certain issues in food security because they are so closely--they're similar to what we have seen with the development of clinical diagnostic assays, and that is, we need to understand how to detect these biological agents in various food matrices which are numerous and varied. How well do these pathogens survive in a given food matrix? Can such a pathogen cause human disease following oral ingestion in this food matrix? What's the relevant inoculum causing clinical disease?

Again, these are questions that are currently of great interest and the subject of a fair amount of activity that we need to develop.

Lastly, I'd like to touch on some issues in radiation safety. This is a little bit different because this is an area where, as a public health community and as a government, we have decades of experience. In fact, decades ago, this was an issue of tremendous interest and tremendous public health preparedness.

In FDA, we maintain expertise in radiological public health. We have experience with population dosimetry studies from one of the largest sources of radiation to the general population, that is, medical X-rays, and as I mentioned earlier, we have a role in radiation response.

The maintenance of a workforce with these kind of skills requires a combination of scientific credentials and on-the-job training. There is some recognition that these kinds of individuals who were very much in demand decades ago are starting to retire. It's not clear that we have identified the sources and the means for maintaining this workforce. And we need to start looking at where this kind of resource is being trained, what are the programs out there, how are we going to identify our next generation of radiation safety workers.

The expertise that the country has had in nuclear and in radiological events may serve us very well, and at the same time we need to be positioned to think very broadly about how radiation exposure might come about when the element of the human imagination is introduced into these kind of risks. What we had traditionally thought were the categories of risk to think about may need to be expanded depending upon what

someone might think is an appropriate medium in which to slip a radiation-emitting material.

So, again, we are looking at a strong regulatory precedent, but a need to maintain that and stay light on our feet when we try to understand the breadth of problems conveyed by new risks associated with terrorism.

By way of conclusion, I think what I'd like to show is the balance we seek to strike in our efforts in counterterrorism. As an agency, we have a mandate to see that any of our regulated products meet a standard of purity, of safety and effectiveness, and are available when they're needed. In a public health emergency, such as would be presented by a terrorist attack, it's imperative that there be a rapid availability of these regulated products for large-scale use.

The agency's role in counterterrorism is to see that this availability need is met for pure, safe, and effective products consistent with our legal responsibilities as a regulatory agency.

Thank you very much, and I will be happy to take any questions.

DR. LANGER: Would you like to do questions now or after Joe Levitt? What's your preference?

DR. MEYERHOFF: I am happy to wait if that--

DR. LANGER: Anything is fine. So we'll wait. Good. Thank you very much.

So Joe Levitt will talk about food safety and the counterterrorism initiatives.

MR. LEVITT: Thank you very much. A pleasure to be here. Let me begin by thanking the Chair for your distinguished service as Chair of this panel and welcoming the new Chair. We look forward to the seamless continuity that we know will occur.

I reflect back to the first time I addressed this Board several years ago following the Science Board's review of our Foods Program. We provided a lot of good suggestions, and today we are well on our way to making a lot of progress there.

Understandably, that review did not really address counterterrorism, that not being broadly on our agenda at the time, and so we have a lot of new information this year.

I think probably my first main point is that today, about a year after the terrorist attacks, while a lot has been done--and you'll see a lot has been done--we also now have enough distance to really see how massive an undertaking this really is and needs to be.

Interestingly, in today's Washington Post, for those of us that had time to get past the detailed description of the sniper apprehension and so on and so forth, on the front page there is a report of a major bipartisan panel on counterterrorism. This panel, for

those that didn't see the article--and I didn't know anything about it until I saw the article, so don't worry, you're forgiven--was chaired by former Senators Gary Hart and Warren Rudman. It had such distinguished membership as George Shultz and Warren Christopher, former Secretaries of State; former Chairman of the Joint Chiefs of Staff, William Webster, former FBI and CIA Director; and Harold Varmus, former NIH Director. And the major conclusion from that report is that, "The task of protecting the nation is so complicated and expensive that the government's multi-billion-dollar efforts will barely dent the problem."

That's kind of a staggering statement and a sobering statement, but I can tell you, for somebody who has lived it from a inside-the-FDA standpoint, it rings true.

My third point is that--and I will periodically come back to this only because I can't help myself. While we have done a lot of planning, a lot of exercises, a lot of laboratory work, we had our own little version of on-the-job training during the anthrax episode of a year ago, not because of the fact that food was affected but the fact that our building was affected. And when we were downtown at FDA--we've since moved up to College Park. Because of our proximity to the Brentwood mail facility and the triage of testing mailrooms, we were

among the first mailrooms in Washington to be found to be called "presumptively positive" for anthrax. That was on a Sunday night. Because that was the front end of what we're now calling the need for surge capacity, it took almost an entire week before we found out on Saturday, confirmed from the Centers for Disease Control that, in fact, it was negative. But it was one hellacious week, and during that week, in retrospect, I can tell you, we learned a lot about what it feels like to be a victim as opposed to just somebody on the scientific end, learned a lot about risk communication, and in retrospect, I think it's been a valuable part of our emergency preparedness.

With that, let me go to what I want to talk about. I'll describe some of our general main messages, the activities we've undertaken, some areas of special attention, and some conclusions.

I think, first of all--and this was one of our first insights about a year ago--was that we're not starting from zero; that, in fact, we have a good start; that the systems that have been put in place to reduce foodborne illness, those systems being the surveillance system through CDC, the FoodNet and so forth, the prevention systems we've put in place, HACCP, good agricultural practices, the emergency response system that's been drastically improved, including the advent of the PulseNet and the DNA fingerprinting--those are the

same systems that will help us preventing and responding to a terrorist attack.

Indeed, when you think about it, if there is an outbreak of foodborne illness, you don't know in the beginning whether or not it is accidental or intentional. We've always assumed that it's accidental, but now we realize it could be intentional as well. But in the beginning, you're not going to know, and those same systems are going to be the ones that we're going to need to depend on.

We've already realized that especially critical is we need to do what we do best. We need to continue to rely on science-based approaches to solving these problems. And if we do that, we do feel we can make a lot of progress.

Now, let me describe what we've done. We very quickly put together what we call a short-term, medium-term, long-term plan that divided our activities into three simple notions. One is anticipation. To what extent can we do risk assessments, threat assessments, to anticipate what is the highest areas of likelihood that food could be used as a terrorist vehicle? You know, nothing is for sure, but to the extent that we can anticipate, we should.

Second, we know we can't anticipate everything, and we're going to have to be sure if something happens

we can respond effectively and immediately. But over the long haul, just as with food safety generally, the more we can put in place prevention/deterrence systems, the better off we will be in the long run. And so we have gone through and tried to flesh these out, so let me do that for you here.

Starting with anticipation, one of the first things we found out--it's interesting, the things you learn in times of unexpected occurrences. While Dr. Meyerhoff is right we're dealing here with a lot of exotic agents that we've not been talking a lot about recently, nevertheless, we have a lot of people with a lot of experience. And all of a sudden you hear, you know: I worked on anthrax 20 years ago; people told me stop working on its because it wasn't relevant. But we found we have people with a lot of experience, a lot of expertise, and we put together special teams to do a series of risk or threat assessments across the food supply.

We used a model that we obtained from the Air Force, you know, under the good slogan, "Good luck beats good planning any day." In the Air Force Reserves is a gentleman named Larry Barrett, who also is in the Department of Public Health in California. He got called up in the Air Force to put together a food security plan for the Air Force. Pilots eat, too, and they want to

have safe food. And immediately because of his civilian work, he realized that the applicability of what he was putting together would have direct applicability to us. So he immediately went to his Surgeon General and his superiors and figured out how to declassify or sanitize, whatever the right verbiage is, and shared with us the system known as operational risk management, which basically looks at a combination of severity and probability and tries to match where is the greatest chance for the greatest harm and really focus there.

We used that system, and we used a three-part process looking at the food, the agents, and the place in the food chain.

Now, it sounds kind of silly, I will confess, but the way we all remember is to think back to the board game Clue. Everybody remember Clue? Colonel Mustard with a wrench in the kitchen? Well, you got to know your food. Are you you're dealing with mustard or plums? You need to know your weapon. Are you dealing with anthrax or are you dealing with smallpox or what? And you need to know the place, especially in the food chain with so much food processing, what agents are going to be killed by pasteurization and which aren't. What happens at the end of the system is different from what happens at the beginning.

And what we found is that it's also a good triage system, because almost any food can be tied to some agent, and almost any agent can do some harm somewhere. But once you start putting all those three together, you can start refining what are the greatest likelihoods.

And we put together a panel of experts from FDA, from the Center and from the field, and we came up with a series of threat assessments internally. That process is now being validated externally by a group through IFT.

Interestingly, one of the things we've learned--there's also reference in this news article--and that we're not used to is the fact that a lot of this information, while really sought after, also needs to be really carefully protected. The watch word is don't give the terrorists a road map. And so those threat assessments, no sooner were they written and we presented them to the department leadership, they were immediately classified. And you know what that meant? The people who wrote them could no longer read them. But don't worry, the safe had them, and they were safe. They were safe from the terrorists and safe from all who could use them, beneficially or un-beneficially. I saw that obviously sarcastically. It was an area of major internal debate and frustration.

A year later, I can tell you we've put a lot of people through the clearance process, and so now the people who wrote them can read them and can use them to our benefit. But one of the things that is new that we are not used to is the notion of secrecy versus the need for openness. And it presents major challenges, I can assure you.

At the same time, or actually before--and we actually had this going before September 11th, although not by much--we had a contract scheduled Battelle to do a similar kind of threat assessment from the outside. We got a progress report on that in the spring. We made some additions and adjustments, added our own experiences, and that final report is due out in December. And so we'll have the benefit of that.

Also under the area of anticipation is better intelligence gathering. You know, I now say all the time, because it just seems so odd to me, that, you know, as CFSAN Director, I never thought I'd stand up before a group and say we need a closer working relationship with the CIA. I mean, who can imagine such a thing? And yet obviously that's now true. FDA is fortunate, through our Office of Criminal Investigations, we do have very close ties through to the intelligence community, the FBI, and, again, once you get the right security clearances, we can get that kind of information. And yet I can tell you

even from the intelligence community, this is not the kind of information they're used to collecting. And so this is some new areas for them as well.

So, number one, anticipate what we can.

Number two, respond to what we must. This is probably where FDA historically is at its best. We have a lot of history of responding to emergencies of all kinds. In this area, I'm thinking back to the Tylenol tamperings. We have applied that. We have conducted under Alan Morrison's leadership a number of emergency exercises, and some the FDA leads, some the department leads, some USDA leads. But there is a lot of effort going into it. I can tell you they are sobering exercises. Each time you learn a lot, but you also realize how many things can happen.

One thing that we learned from the anthrax episode, I can tell you both internally and just watching, is the laser-like focus by the media. You know, when you have a foodborne illness outbreak, while, as I said and it is correct, we're responding quicker than ever, nevertheless, it takes time to do the epidemiology. By and large, these things are, you know, subterranean. Nobody knows they're really going on, and only at the end when we announce the recall, ah, you know, the government did its job.

Well, if the media were following us hour by hour, like they were during anthrax, like they were during the sniper episode the last three weeks, you know, it's an entirely different story. And so when you go through these exercises, it is a sobering experience of how much there is to do and how important the work is. But we benefit each time.

A second point that is getting a lot of attention now, as it should, is the whole area of lab capacity and what we're calling surge capacity. Again, going back to the anthrax episode, it boggles my mind that during those several weeks across the country there were over 100,000 samples taken and tested and screened for anthrax. You think back to that time, everybody saw white powder. Everybody collected it, called the hazmat team, sent it in. But the labs couldn't handle it, and, of course, the labs also, as we found out later, didn't have the right test for it. And that was a big problem.

And so the CDC has worked hard through their laboratory response network, through clinical laboratories, to learn from that experience and build on it. And we're also realizing that those labs are not really equipped to deal with foods, to deal with testing of the food matrix. They don't have the methods, don't have the experience, don't necessarily have the know-how, and that is presenting a major, major challenge for us.

Finally, informing the public. As I've referenced a couple of times, these are the kind of events that will get attention like we have never seen before, and the importance of good communication, of constant communication, of knowing who your spokespeople are, I can tell you what we learned internally from just dealing with our own employees. And if you go back to your risk communication manuals it's all there. It just doesn't sing out to you until you've really experienced it as such. You know, especially a scientific agency like ours, we want to have the facts. We want to know the answer. We want to be up there standing--we know Listeria in this product, and these people shouldn't eat it, and we're recalling it, and the thing is taken care of. That's what we like to say. But the problem here is we're not going to know. For a long time we're not going to know. And at that time, it's not about conveying information. It's about building trust. It's about building trust with the public, that you'll be open with them, that you'll be honest with them, that you'll tell them where there is a problem, because basically they think we will not.

You know, think back to alar in apples. All the government people said they're safe, apples are safe, apples are safe. Meryl Streep stood up, took an apple out of the refrigerator, threw it in the basket, and

everybody in the country did the same thing. And so the importance of the right kind of public communications is critical.

Finally, most importantly, but also most long term, is the whole issue of prevention and deterrence. Imports is an area that all government agencies involved with that are critically worried about. Interestingly, it's highlighted in the report I just referenced this morning, across the board, not focused on foods at all. And a major part of the resources FDA provided are geared to strengthening our role at the borders, and that's needed. There's also increased emphasis on laboratory testing, but really an important area that is only starting to receive--I can't say enough attention; it's starting to receive some attention--is the whole need for broad research agenda. And Dr. Meyerhoff covered a number of the points, but as a lot of things, we don't know basic stuff. We don't really know what the--in anthrax, for example, what GI anthrax really is, you know, what its likelihood is, what its severity is. We know more about inhalation, more about cutaneous. We kind of jump through quickly to GI anthrax, but when, in fact, in a survey of the literature, not as much is known as people thought.

We need to know more about how these agents act, what diseases they cause, how to detect them, what

medical countermeasures are needed to respond to them. This is a whole enormous area. In our kind of smaller world of FDA and laboratories is the area of methods development. There is a massive task to be done, and, unfortunately, in the world of research, it's boring stuff. You know, methods development is not where the Nobel Prize is won, but we need to be able to devote enough of the research dollars and interest so we can do our job, so that if there is an event we don't have presumptive positive on Monday that the milk supply is unsafe, only to find out six days later that it was all a mistake and all for nothing, didn't have a good test. That is not going to wash, I can assure you.

The areas of special attention. Number one, we have been fortunate. During this time it was quickly recognized that large parts of FDA, but especially the food section, the chronic under funding that has been circulating in Congress, really came to the fore. People understood why we should be worried, and as Dr. Meyerhoff pointed out in her slides, roughly two-thirds of the supplemental appropriation went to the food area. Almost all of that, appropriately again, went to the field, and most of that has gone to the border. We now have more people at more borders. We doubled the exams at the border this year. We're doubling again this year. The Office of Regulatory Affairs is truly to be congratulated

for being able to hire over 600 people in just a few months, get them trained, up and running, working productively. It's really something of historic nature in the FDA.

In the food area and in the field, not since the early 1970s and bon vivant have we seen this kind of hiring and new blood brought into the FDA. Obviously, not only will it help us for this immediate issue, but the leaders 20 years from now will be from the class that was hired this past year. And they are a good class and we are very proud of them.

Second, legislative authorities. We received the benefit of new legislation, and I'll go over a little more of that in a minute. We also devised a guidance for the industry, what steps they can be taking in their own establishments to reduce the risk. And finally, strengthening communication and coordination of other federal agencies. That's always an issue. Even an article like this that doesn't mention our Department or the FDA, does manage to say there is not a single food agency. And so we're used to seeing that and reading that everywhere, but I do want to assure you, we do talk regularly, we meet regularly. There was a lot of coordination among the federal agencies, but like so many issues, it does take work and it does need constant nurturing.

Let me focus a little on the new legislation. The areas, while there are five major title areas of the legislation, only one of which deals with food, and in the food area there are over a dozen provisions. The four areas that are getting the most attention because they need new regulations from the FDA have to do with these four areas. Number one, registration of food facilities. Many people are surprised. "You mean that didn't always occur?" In a drug area you have to register with the government. In many other areas you have to register. Not in the food area, so that's new. And that covers all the products we regulate, food, animal feed, dietary supplements, the whole shebang, and also includes for establishments. The challenge is for a place that didn't have any registration, now we're looking at registration of upward to 300,000 facilities. And so that itself is a major challenge, not just the right regulations, but to have the IT systems in place so we can pull that off.

Second is the establishment and maintenance of records. This has always been a major bone of contention with the food industry. Again, in the drug industry it's relatively accepted because it's been part of the law for so many years. In the food industry they're my records. They're my records, they're not yours. And you know,

basically when you get a criminal search warrant, you're going to get it and see records.

But recognition, the time for that has come and gone. If we are to have rapid containment of an outbreak, we need to quickly be able to trace back where the food came from, and if it's a problem at a facility we need to be able to trace forward where it went to. And so there is new legislation to require a step-wise maintenance of records, of what they--it's basically described as one up, one down. You need to keep a record where you bought it from, where you sold it to. And then the next person along the chain has to do the same thing, so that there ought to be a chain back and forth. It will not be foolproof. There are lots of areas that are not so susceptible, where products are commingled. You may know where you see it, but at the end you're not going to know which one started from where, and ingredients are commingled at manufacturing sites. So it is not a foolproof system, but it is a system that will be significantly improved over what we have now.

Third, imports. Again, major interest in imports, a system for prior notice of imported food and shipments. We're getting now, what, John, 5 million, 6 million entries a year. That's a lot of food coming across the border. And the notion is if we had prior notice we could better triage and decide what we really

need to look at, and finally be able to detain goods, an administrative detention mechanism, so that if there is a problem--and this is largely domestic, because we do have that authority at the border, that we could, instead of running to the state officials, which we do now, and say, "Can you put a hold on this while we go to court," We would be able to do that ourselves. We have that authority in the medical device area, so FDA has some experience with how to do that. All of these regulations are on a--for lack of a better phrase, a really fast track. The reason is not just because the law tells us to do them, for better or for worse, there's a long history of statutory deadlines. Some get met, some don't. But the ones that get met, I can assure you, are the ones that have a hammer, meaning if you don't meet it, something even worse happens. And under registration, if we don't have regs out on how to register, they still have to register or the food can't be sold or imported, and that's a pretty heavy hammer. So we will have a registration system in place I can assure you.

Same with prior notice. There will be a prior notice system. Both of those December 12th, 2003. That's only a little more than a year away from now. There will be one in place because they are required by law, where they may not import their goods. So I sure

hope, since they can't import them, and we don't want to have a line at the Mexican border all the way down to Argentina, which is where it would be in about 5 hours I think. We are going to have to be sure we have that in place. So a lot of effort is going on into that.

Guidance to the industry. I reference this quickly. This is one of the things we're able to do early on, and have gotten a lot of positive feedback on. We have guidance both for domestic producers as well as for importers. They are designed to be preventive measures. One of the areas we got a lot of feedback on was retail area is really different in many ways from a manufacturing establishment, the most obvious of which is, when you think of intentional contamination, the most important thing is access, who can get in. Well, in a food manufacturing plant, you want to keep out people you don't know. But think about your local food store. You want people you don't know coming in. How else are you going to sell your products? And so there are some significant differences, and so as we go through the next round of guidance, we'll be doing something specific with year two, the retail community, and we've had a lot of meetings with them on that.

I want to pause here, and let my energy level go down a little bit. When we first started, I guess the first presentation of this type I gave last December, and

that was--I mean last fall was such crunch time, I can't even describe it because I don't think my mind would be clear enough to be able to try and describe it. It was just constant overload. And you know, the period it looked like, when you start seeing how much there is to do, the food system is so wide open, it is not geared to protection of this type, that it almost feels, I mean, it almost felt overwhelming, and you wonder, should I just give up? Should I just say we can't do this. Go and create and Department of Homeland Security, staff them up, let them do the right thing.

And so we kind of paused and took an inventory, if you will, what are our assets or what do we have going for us? And we realized we actually have a fair amount. Number one, we have a lot of capability and know-how, as I mentioned earlier. Not only do we have a lot of good microbiologists and toxicologists and chemists, but we have people that have varying backgrounds. You find the people that have been to the military, people that have gone parts of their career through CDC, infectious disease areas, and when you take that, you add what's known in academic institutions, you add what's known in the industry. There's a lot of capability and know-how in this country. And realizing that, I think was positive point number one.

Positive point number two is that we do have nurtured and believe we have a positive relationship with the industry we deal with. To be honest, I was a little worried that the legislation would become so acrimonious that might pull away. We're able to keep that under control. But by and large, this is an area you have to be able to work with the industry on. This is something we have a joint problem, a joint enemy, and indeed they had joint resolutions, and we feel good about that.

Third, the FDA has a long history of successfully responding to challenges. Part of our culture, part of who we are, part of why we work here, part of our heritage, if you will, is we do rise to the occasion. There's lots of examples of that dating back to 1906, most recently successes on food safety that I ascribed earlier.

And finally, there is a lot of public trust in the FDA. I talked before about credibility and public communication. The public does believe the FDA and we'll need that, and the FDA does have a very strong esprit d'corps and ability to rise to challenges. So this is a little bit of true confessions, but once we kind of catalogued these, we said, "Well, wait a minute. We can do this. We can do this too."

In conclusion then how do we kind of reflect on this? I think number one, food safety and food security,

while there are differences certainly, they are closely related. As I said, the same kinds of systems and approaches that have worked well in food safety are going to help us here too. Number two, FDA is certainly increasing its vigilance. I think that by now that's an understatement. Three, this is under-anticipation. We need to be prepared for what is reasonably foreseeable, and we spend a lot of time trying to understand what might be reasonably foreseeable. But, four, we can't figure everything out in advance. We have to recognize that unexpected things happen, and the way I think of it is, you know, you have your forward sight for what you're looking at, but you also have peripheral vision. And when something happens out of peripheral vision, you need to turn to it, and now that's in your central sight. We need to realize unexpected stuff is going to happen, and that's when you rely back to what are your assets, what are your tools, what are your underlying capabilities. And then finally that means is we need to have the flexibility to respond swiftly and effectively to anything that does occur. God forbid that it does.

With that I am happy to, I guess, welcome Dr. Meyerhoff back up here with me to help answer questions across the spectrum of our issues. Thank you very much.

DR. LANGER: Thank you. Why don't we open it up for questions, comments?

MR. DOYLE: Thank you very much. I really appreciate the comments. I thought that whole presentation was very well done.

Mr. Levitt, for you, I continually hear and agree that imports are probably one of the our real soft spots. Is the Agency taking a holistic size-based approach to inspection of imports? Are we profiling, based on science, the greatest foods of risk? Are we determining, based n science, the best sampling methods, as well as the best testing methods and taking advantage of science to do all this?

MR. LEVITT: Obviously a good question. The answer is, that's a work in progress. That's certainly our goal. And you need to also add in there what you know in terms of triaging from where the food is coming from in terms of what are hot spots. This goes back a little to the threat assessments that I described that we did that were actually designed to do that. When we locked them in the safe, it became harder to do it. We now have more access to the safe, and so you're going to see more of that rolling out. And because even though we have increased--this will be confidence inspiring--we've increased the sampling from 1 percent to 2 percent. That's why we say we doubled and doubled again. It does sound better.

[Laughter.]

MR. LEVITT: But we're never going to have high percentages. That's why targeting, triaging, stratifying is the key to be able to do this. I think in its first phase, to be honest, more effort has been gone just getting more people out there, getting them trained to know how to do this. As we gear up there will be more triaging. As more intelligence information comes in, we'll feed that into the system. Part of the new IT systems I describe for registration and prior notice are really part of an ongoing upgrade across FDA through ORA, through Regulatory Affairs, to upgrade our OASIS system, which is the historical import system we've had that itself tries to triage our internal, our domestic information that we have. We're trying to get that all brought in together so we have, if you will, a centralized, computerized brain of information that can help triage.

In terms of the laboratories, the ability to follow up on the threat assessments will depend on having the right methods, the right laboratories, the right capabilities. So we will phase that in based on what we do have. But it will be some time before we have all really the right tools so that the work at the border--that's really the bigger picture. I think last year while we were putting together the appropriations, during that time of enormous intensity, I guess what I learned

in retrospect, in times of enormous intensity, you get one message. And the one message that got out was FDA doesn't have enough people at the border.

The concomitant, which were I to do it over again, I would have found a way to package two halves of one message, is you've got to have the people, you've got to give them the tools. And the scientific tools, which is what you're referring to, is something that the funding was, you know, not proportionate by any means, and something that we're really trying to focus on in coming areas.

There is some opportunity, assuming the 2003 budget goes through. The National Institutes of Health have received, from an FDA perspective, an enormous amount of increased bioterrorism funding. Some of that may be an opportunity for us, because they do have an area--we were just briefed a couple weeks ago--they have an area for diagnostics. And while they were thinking originally human diagnostics, as we talk to them, they understand the point that you need to be able to have the diagnostic for the food as well as for the person. And so those of you from academic institutions, the FDA cannot apply for those grants, but it's something we'll be working on getting the word out that that is an area to try and tap into.

DR. LANGER: Yes?

DR. DAVIS: You mentioned Category A agents in particular, but of course, as far as the food supply and certainly for things by the oral route, Category B and C have the agents that are actually of far more concern perhaps than even Category A if you're going to swallow things. Can you comment on where you are in terms of the full spectrum of those categories?

DR. MEYERHOFF: Sure. I would say two things. First of all, the entries on Categories B and C are lengthy, and as you very appropriately point out, are often more of a threat to food than some of the really high visibility organisms I put in Category A on the slide. And truly what we know historically about what has been introduced into food intentionally in this country has been the more garden variety good pathogens. I think particularly of an event each with salmonella and shigella.

The second comment I would make is currently we in the federal public health agencies that are looking at this, are starting to work through Lists B and C, and they are getting a lot of attention right now, both in what belongs on the select agents lists and how we're going to approach dealing with those bugs. So they haven't been neglected, but rather left off of my presentation more for the sake of showing what are some of the highest threat agents.

MR. LEVITT: If I could just add to that. From the food perspective, what we're calling the traditional agents like salmonella, E. coli, listeria and so forth, we're more comfortable simply because we have more experience, we have the tools, and we're more just better prepared to deal with that. But one area, now that we think back to the food safety activities over the last several years, one of the areas that was really missing was medical countermeasures. There really was not a lot of interest or attention to medical treatments for food poisoning, and I think that may be one positive side effect of this now that people are thinking of medical countermeasures. Before it was simply find it, bring them in, give them antibiotics and go home. Now there may be more interest in dealing with some of the medical countermeasures that weren't really in the medical arsenal before.

DR. DAVIS: That's somewhat, you answered one of the questions that I was going to pose. $159 million didn't seem like a lot of money as you listed out all of the things that FDA was going to be involved in, et cetera. It seemed like a drop in the bucket. And even though NIH may be getting a lot of money that you say you may be able to piggyback off of. Obviously, when it's other people's money they get to drive the program, and

their interest and yours may not lie along the same length. So that was one thing.

But the other thing that was mentioned about the availability of nonhuman primates to potentially do some work, clearly, that takes a lot of money. My business in drug development, we're always scuffling now with the availability of primates to do normal drug development. So to have someone like FDA out there using those same resources, that's not something that's going to be doable in a quick fix kind of thing. And so you'd have to be a sustained user in order to increase the supply, and that again will take I think a lot of money. And so my concern was that 159 million, sounds like most of it is going over to people to do the border work, which I'm sure is necessary, but how do you get the rest of that done, and what do you sacrifice? What else isn't being done in order to do this new work? It just sounds like there are a lot of activities that you have been engaged in in the last year, so what hasn't been done?

MR. LEVITT: Well, let me kind of go back to, for better, for worse, the world of the federal budget. And I guess one I've learned is that it is very difficult to break out of historical norms. The FDA is, by federal agencies, is a small agency. And a lot of budget talk is in percentages. And so while we joke and say we'll just take 1 percent of the NIH budget, we're not allowed to

talk in those terms. You know, a 10 percent increase in the FDA budget is like what more could you possibly want? And so the FDA, that's part of our world. As a second part of that world, in the food area, there was a GAO report, by now a couple years ago, that pointed out that the FDA has 80 percent of the responsibility in food regulation, but 20 percent of the resources. So along comes the Bioterrorism Bill. They do appropriations. The FDA got $100 million for foods. My gosh, you broke out of that mold. Well, USDA got 400 million. You know what that is? 80/20.

And so somehow the system does not break out of traditional modes. We constantly fight against that. If you have any ideas, but I would just tell you, that is a nature of the system. I was--I guess even I took a step back when I heard a presentation from NIAID, where a lot of bioterrorism money has gone, appropriately. Their increase, increase at one institute, a big institute for '03 if it's passed in the President's budget, is 1.75 billion. The FDA budget, not the increase, the FDA budget for everything we do is less than that, a little less than that. It's the same ballpark. What are we at now, 1.6 maybe, 1.6 billion. So an increase is greater than our entire? What that tells us is that one, we have to keep making the case, but we also have to realize we have to really go to leveraging. We have to be good at

working with programs that are elsewhere. We cannot think of it simply as the FDA is an isolated island. And a lot of our work is based on working with USDA, with the research that's done internally at ARS over there, extramurally through CRES [?] and tapping into NIH funding and working with universities. That is part of who we are and how we work, because I think the other, if we think we can do it all by ourselves, I don't think we'll ever get there. In terms of what is not getting done, we worry about that all the time. I can tell you that we all feel that the food safety work that had increased for several years, has--I would say that momentum has paused. We haven't lost the momentum, but it has not continued to accelerate as it might otherwise have done. We do need to respond and are doing incrementally more work in areas like food allergens. The TSEs is an area that is getting more attention.

But you are absolutely correct, at some point there is only so much in that box to give. And what we keep looking for are areas that we get a two-for out of. When we put somebody at the border, they're not just looking for anthrax. They're looking for additional agents. They're looking for the same work we've also looked for, so a lot of it does go for both, but you raise important points

DR. MEYERHOFF: I'd just like to add a couple of things to Mr. Levitt's remarks. On the issue of leveraging on the medical countermeasures side, I think recognizing that NIAID has been very well recognized as a place where the research dollars are going to go for the development of research and new products, we work very closely with them developing criteria for animal models and looking at what needs to happen to study these new products, vaccines, immunoglobulins, drugs.

Yesterday I was listening to some remarks from Dr. Fauci, and was very interested to hear what a large proportion of their efforts are going to go towards product development. They are looking for deliverables that I think we, as the regulatory agency, will be deeply involved in.

Your comments about the primates I think are very well taken. One point I want to make explicitly because I'm not sure I did in my remarks, is that we are not so much seeking to have animals on which to work in our laboratories, although we do do some of that, but rather, I think because we think see the breadth of product development, we understand how many different products are going to need primates. And I think we need to collaborate with the academic community, with industry, with the other federal agencies that are working on this to recognize we have a limited resource,

we need to figure out what comes first and what comes next, and make sure that we deploy it in a way that serves all of these needs. So, yes, there's a shortage of those animals and it's going to take a lot of organization to figure out how to use them best.

DR. LANGER: Yes?

DR. RIVIERE: Mr. Levitt, following up on this increased vigilance at the border, did you find out anything with that? I'm curious because the sampling has always been so low and now that you have an increased presence for non-bioterrorism type of problems, have you come up with anything that was a surprise or--

MR. LEVITT: I guess I'll ask John to see if he has more specifics on that.

MR. MARZILLI: Yes. The first thing I want to mention about the increased vigilance on the borders, I know a lot of people probably came in through National Airport or Dulles Airport this morning when they arrived here, and they were greeted by folks from the TSA. That's not the kind of employee that we have at the border.

First of all, the folks that we hired in the counterterrorism hiring and in our additional hiring, are all folks with science degrees. Most of them have experience. Just f.y.i, the average age of these 600 employees that came in was 36, so we have a lot of people

with a lot of experience. These folks are not strictly deployed at the borders. That is their home station. That's their home office. But these folks will and are also conducting domestic inspections at the plants where these products are further manufactured in the United States, and going overseas. So they will be going overseas to do inspections at overseas that manufacture products for here.

Yes, we have had a number of very interesting cases this year in terms of folks that were familiar with products, and just having hundreds more people on the border as a border presence, looking at these products come across, could be things as simple as the person conducted an inspection at pharmaceutical plant X and new what the raw ingredients were that were going into that firm. Yet, they saw an entry coming into the country that didn't look anything like the drums of raw materials that were destined for that firm. That makes a completely well rounded investigator that we have there on the border. And as I said, all of these folks are folks with science degrees, and we have had a number of interesting cases this year, and even things as bizarre as crates of product coming in with something sprawled on the side that says "Osama is our hero." I mean things like that, having people there has made the difference,

and having product testing done at the border is additional work that we're doing as well.

DR. RIVIERE: Well, I guess the question is, is the sampling before was relatively sparse, and I'm wondering if that's increased now because there's increased testing going on pretty much to those predictions that were holding before as to incidents that carry through. In other words, were there any surprises? Were you all of a sudden finding an increased level because of more people looking in say a specially specific commodity area, an increased presence of either bacterial contaminant or chemical contaminant? Are there increases again of chlorine pesticides coming in?

MR. MARZILLI: Actually, that is a very good point because we have--as Joe has pointed out, these efforts are dovetailed with our domestic efforts, so we have had more, quote, "hits" in terms of some of the pesticide problems that we've found and some of the pathogens, not only natural pathogens but the foodborne pathogens that we traditionally look at. So we are getting a lot more surveillance. As we're implementing these counterterrorism efforts we're getting a lot more surveillance on the front in terms of food safety and safety of other products as well.

So, yes, we are finding--we're getting more information. We're honing in on more products. We're

able to do more blitzes as a result of it, just because of the intelligence that we're gathering.

But, yes, we have had increases in pesticide residues, increases in finding products with some contamination from heavy metals that we may not have had a chance to look at before because we simply didn't have people out there collecting the samples.

Our sample examinations this year, as we cranked out the numbers, went from about 10 or 12,000 last year to I think it was 34,000 sample exams at the border this year. So, obviously, what that is helping us to do is to better target products as well as things are progressing along. And we have a system for doing that through importer lists, et cetera. So it has given us a lot more information.

And it's been good fortune for us that some of these systems, as Joe mentioned, the OASIS computerized system for import entry that was developed a dozen years ago to facilitate product entry into the country with more people tuning in to their computer screens and taking a look at the products as they're coming across, and being at the border with that information, querying other data systems, has really given us an opportunity to do a lot more surveillance, and we're going to be cranking that up again next year, so it's been a dual win for us, actually.

MR. LEVITT: There's also, I would just add, an intangible element as well, and that is having enough presence, enough show of force that this does not come across as the weak link. And when we--when you stand up and say there are 300 ports of entry and the FDA has 150 import inspectors, how do you say that to the public if you're really worried? You know, the FDA had always seen the import program as a check, a small little check as opposed to a first line of defense. And so that difference, it's hard to measure exactly how much--what the impression is on the other side, but they'll see if it's harder to get through, if there is more scrutiny, then they are less prone to just think it's an easy mark.

DR. RIVIERE: Would the creation of a Department of Homeland Security impact any of what you just presented?

MR. LEVITT: I don't think so. One of the things that we have a done a lot over the last 5 or 10 years is work more closely with Customs Service, and while the U.S. Customs Service is to be part of the new Department of Homeland Security, I suspect they will remain much as they are, and therefore, our connections with them will remain much as they are.

DR. RIVIERE: Thank you.

DR. DOYLE: NIH has a major request out now for proposals addressing a foodborne and waterborne network,

which I guess would try to line up several universities and perhaps other facilities throughout the country. Is FDA an integral part of this program?

MR. LEVITT: That really was part of what I was referring to before, and we have met with them. Actually some of the people working at NIH came from FDA. One of them actually came from CFSAN. And so I think they've made real overtures to try and understand what the needs are so they can respond properly. But as somebody said, it's not the same as having your own. We have to learn how to work within that system. We in the food area are not as familiar with the NIH system, the study sections, how they review the grants and so forth, as other folks may be, so it's a learning process for us.

DR. DOYLE: Following up on that, it seems to that FDA ought to be a highly important player in this approach, because as I read it, there's going to be kind of like an oversight, an overseer, whoever that may be--it didn't indicate in the grant proposals--but they're going to determine what additional testing may need to be done in the case of an event, and who would get involved in development of methods for detecting foodborne pathogens. This all seems to fit very closely to what your needs and interest would be. So I would hope that FDA could be a primary player, not only in the end product, the end results of all this, but also in the

developmental stage in identifying besides the key players.

MR. LEVITT: I agree.

DR. LANGER: Are there other questions anyone in the audience or FDA would like to ask, or comments?

[No response.]

DR. LANGER: I guess not. Thank you very much. That was really very, very helpful. Is there anything that we can be helpful to you on?

MR. LEVITT: I think for us your words of encouragement on the research side and the method development side, as I said, funny things drive budget allocation, and while we like to think there is some cosmic risk based thing, that's there in part, but in part, certain projects require certain sums of money. You're going to put in an automated food registration prior notice system, that is going to take a chunk of money. But it has a definable amount. And so you can say, "This is what I need and I'm done." The area of research, methods development, is a little more amorphous. You can't say, "Give me $5 million and you will never see me again." In fact, the worry is there's a never-ending need, and so whatever I give you is okay because I can't satisfy you anyway.

Any help or advice you can give in how to help us frame research needs, relative importance to other

things, so we can keep that high on the radar screen, I think would be very useful to us.

DR. DAVIS: That sort of goes back to my concern about the vast array of things that we put up earlier that the FDA saw it should be involved with around this topic, and the fact that there was only $150 million. Any organization has a mission, and people always look to see where they can be involved and have a real impact. So I think one of the things that FDA's going to have to do in the absence of being able to get real dollars, as you describe them, you're really going to have to prioritize the programs because there are a lot of things to do, as you put up in your list, but $150 million are not going to go very far unless you start to cut into programs that were already ongoing. And maybe you have to do that with something like this, but again, I simply say what last year, what was very important is no longer important, that you can get rid of it to carry out this program. And that's of concern.

MR. LEVITT: Just to give you some sense of the portion, in CFSAN's research program, we consciously decided we would redirect 15 percent of our research program to methods development for these areas. So from an inside viewpoint that's a lot, because it's not 1 or 2 percent, that it affects a number of different people in our center, but it also means 85 percent we didn't

redirect. That will give you some sense of proportion that way.

DR. MEYERHOFF: If I could just make a couple of more comments on that. You're right, there is a lot to do, and I think there's a number of different tools we can bring to that. Some of these tasks are built into what we already do. We do a lot. If we had more, we could do more.

Secondly, we leverage across the government and other sectors of society, with industry, with academia, to get some of these jobs done.

Lastly, and probably what I think is really one of the most important things in counterterrorism, is understanding the need to be light on our feet. We are never going to be able to predict exactly what the next event is going to look like, but we need our systems to be elastic enough and moveable enough that we can respond, knowing what our job is but not knowing what the exact threat is going to be perhaps until very close to the time it happens or when it does.

But your points are very well taken. Thank you.

DR. LANGER: Other comments?

MR. LEVITT: I'm sorry. Could I add one other thing in response to your question.

DR. LANGER: Sure.

MR. LEVITT: Another area that you could help us with, and maybe it might be a topic for the next meeting, is how we can better capture the expertise out in the many universities in the country. We are--I can't say starting because it started--to receive a series of visits from University X with their new Center for Food Safety and Security, and University Y with their Center for Food Safety and Security, and Z with, guess what, their new Center for Food Safety and Security. And while they're all coming hoping to get funding and are sorely disappointed when I describe our funding capabilities in the area, nevertheless, there are a lot of established universities with established expertise, which if there is a way to get that banded together--NIH often likes the phrase "Centers for excellence"--into a series of Centers for Excellence in Food Safety and Security devoted to these things, so we're not duplicating, so we can tap into the right people, and so we have more of a real forward-looking effort, that's something that I think would be worth further discussion.

DR. LANGER: I think that would be very useful to a future meeting.

Along those lines, one thought is--this is really only a partial answer to that--but is giving talks at scientific meetings in universities. I don't know to what extent that happens, and I would think that if there

are scientific talks on these topics, they would probably make you much more visible and people would be interested in sharing things with you. I don't know if there are really programs aimed at that or not, but that's just like I say, one thought.

I'm sure the people here are all at universities and would certainly be happy to help. But if you let universities know, I mean I'm sure that there's some interest on the FDA's part. I'm sure that they'd be happy to invite you.

MR. LEVITT: Thank you.

DR. LANGER: Other comments?

[No response.]

DR. LANGER: Well, thank you very much. What we're going to do is take a break and then come back at 10:15, where we'll be discussing the Office of Cellular, Tissue and Gene Therapies at that time. Thank you very, very much.

[Recess.]

DR. LANGER: The advice I'm getting is that when people want to speak, they need to press the button and make sure the red light's on, and then they can speak, reasonably close to the microphone.

With that, let me introduce Kathy Zoon, and she's going to discuss the Office of Cellular, Tissue and

Gene Therapies. I'll let you lead the next discussion, Kathy.

DR. ZOON: Thank you.

I just want to say it's a pleasure to be here today and have the opportunity to discuss the Office of Cellular, Tissue and Gene Therapies and some related topics, and in doing so, before I get started, yesterday CBER had the wonderful opportunity of having a number of you from the Science Board visit our center, and we had just a great afternoon. For those of you who didn't get a chance to come this time, we're happy to have you all the next time, and we'll certainly be happy to host other visits to CBER, but we had a great discussion, a lot of very good input onto the programs that were presented, as well as some of the specific projects and initiatives going on in CBER. So thank you.

My presentation here today actually is a reflection of a lot of thinking that you all have done with respect to cell tissues and gene therapies, and the discussions we've had previously with this group on combination products. And CBER has taken to heart the discussions of this body. We've had a number of open public workshops regarding cells, tissues and tissue engineering with Dr. Feigal, David, and have spent a lot of time thinking about this.

And one of the fruits of our discussions and with the support of Dr. Crawford, has been the creation of the new Office of Cell, Tissue and Gene Therapies. And in saying this, one of the things that we are currently doing is working with David and CDRH on tissue engineered products, and we are currently working on a schema that we will hopefully have an opportunity to present to the Board at the next meeting that will look at the issues and how we are going to manage these as a seamless process between the two centers, so that these products of tomorrow can actually reach patients in a timely way.

So, David, I thank you and all your team, and we look forward to continuing to work together on this important area.

I just want to spend the time this morning discussing several issues, to talk about the regulation of biological products in general, and some of the philosophy which I think is really important for products of new technology, including the products that are in the new Office of Cell Tissues and Gene Therapy.

As you know, the regulation of our products is based on science, law and public health impact, and this has really been afforded us by two main laws. It's the Public Health Service Act, and the Food, Drug and Cosmetic Act. And I think one of the things that CBER

has looked at over the years is the importance of science underpinning our regulation of these products as well as making sure they're safe and facilitating them to the public.

At the core of this you'll see research. Research I think of, there's two pieces of research. One is a laboratory based science and another is the research that one gives intellectual freedom to our scientists to think beyond the boundaries and to contribute to new ideas and new processes. So in our center this has been the core of our mission with the review process and our surveillance in policy and compliance.

In doing so, I think it's important for people to realize we have four main product offices within the Center for Biologics. We have the Office of Therapeutics Research and Review, the Office of Vaccines Research and Review, the Office of Blood Research and Review, and now the new Office of Cellular, Tissue and Gene Therapies.

While CBER is constructed on an office level, the dynamics and the interplay between our organizations is intense. We feed the science across our organization. We're not a stovepipe organization. We're actually a very cross-cutting organization with respect to sharing science among our agencies. We have focus groups. We have cross support for all our products, and I think I will come back to this because I think some of the

reorganizational changes that have been proposed that we are working with Dr. Crawford on have raised grave concerns with me. And I think I will discuss those to some length during the course of my presentation before I turn it over to Phil, and perhaps this is something that the Committee will discuss with me. So with that, I will go on and talk about why we actually went in and established this office.

The first question is why did we actually create this new office, and one of the main reasons was because there was an increasing number of regulatory activities in this area of cell, tissue and gene therapy. In addition, we were looking at stem cells and tissue engineering, and how to incorporate these important products into our organization in a way that we could facilitate science.

Now, clearly in the area of stem cells, we have been working with stem cells for quite a while. We have had peripheral blood stem cells, cord blood stem cells, mesenchymal stem cells, a lot of different stem cells. However, most recently back in August of last year, President Bush allowed that embryonic stem cells created before August 9th, 2001 could now be used in the public forum to do research. So the opportunity to look at tissue engineering in a global sense, and really to try to understand the science and how we were going to move

this area forward became a major new program for our center. We were also seeing that these products are getting more and more complex. Dr. Noguchi, who will be the Acting Director of the new office and will speak to you, will give you some examples. We're just not talking about a cell. We're talking about how these cells are grown, how they're manipulated, what are the factors that cause their differentiation, how do you stabilize these, how do you actually understand what the characteristics of these cells are that you can make products consistently? All of this requires a lot of science and a lot of direction in this new area.

And clearly, there's an evolution likewise within the Center for Devices, where new matrixes are being developed and new science is being developed that has to interdigitate where there are combination products. And so we recognize that this is an important area and needs serious attention and work by the FDA. And we are committed to do it, which leads to the seamless and transparent coordination and communication. I think we have heard loud and clear from our advisory boards, from the public comment, that we need to develop a process that is clear, transparent, logical, that imparts the best from CDRH and CBER to get these products reviewed in a timely way, and that we give timely guidance and instructions.

And as part of this reorganization in CBER, our commitments in working with CDRH in developing this process are currently under way, and we look forward, as I said, to sharing that with you soon.

This just gives you a sense of the products that have been coming to this area. We have literally over 1,000 types of cell and gene therapies applications, INDs, into the agency. While there is still not a lot of licensed products available, they are advancing in their clinical investigation. There's also a great advance in the science, so it's an iterative process, and it's extremely important that that CBER keep up with the science, i.e., our research review model, and I think it's really clear for us that you need to have people that understand the science that actually do the science that can help lead the way in developing policy and guidances, not only to ensure safety but to further the science along.

So clearly over the past six years there's been a large increase in this area, even in spite of some major issues that have been raised. Clearly in gene therapy, the death of Jesse Gelsinger [ph] has raised issues. The science is there. It needs to be actually augmented, basic research in this area that feeds into the FDA that we could use working with our colleagues both in government, such as NIH, where we have a lot of

our laboratories, as well as with the industry and academic institutions that are developing these products. So I think we're looking at a very interactive development process.

So what is this new office going to do? Well, this new office is going to be responsible for conventional tissues. These are banked human tissues. And ultimately, as our tissue rules go forward, these will probably encapture reproductive tissues as well. We're looking at assisted reproductive technologies which is the complex manipulations of eggs and sperm and how they're going to be used in the future, as well as i mentioned, the tissue engineered products and stem cells. It will have all the cellular-based products that are currently regulated by CBER in these tissue-based products, gene therapies, xenotransplantation, which is the use of animal tissues, cells and organs. This is a particular area where we have now an advisory committee under the Secretary of HHS to deal with the unique zoonotic agents that might be of some concern.

We have, as I mentioned, the assisted reproduction area. To give you an example of this and some of the things going on in this area that raised FDA's attention to being manipulated in a way that we consider has important safety issues as well as in many ways looking at the success of these processes, where

people are taking older women's eggs and actually taking out the cytoplasm and putting in the cytoplasm of younger women's eggs. And in fact, as many of you know, there's mitochondrial DNA in the ooplasm of these eggs, and in fact you're doing essentially gene transfer in some of these activities by introducing new genes.

So I think there's a lot of issues going on here. Clearly, the combination products is a big area that we are concerned about, and we think that this is really important, and are anxious to move this area forward. Obviously, we want to assure the safe identity, purity and potency of these products.

The expertise. We've had a lot of input from you on the Science Board. We thank you for that input. Many of you have contacted us with your ideas, and so this is still evolving, but some of the expertise that this new office has is in molecular and cell biology, viral and nonviral gene therapy vectors, nucleic acid chemistry, genomics, proteomics, tissue and organ regneeration, developmental and reproductive biology, stem cell biology and physiology, obviously, our clinical expertise and pharm/tox.

We look at our ability to regulate in this area as one that's going to require a lot of outreach and get a lot of scientific input, because clearly all these areas will have an evolution, and the Agency cannot

handle this all on our own. We're going to have to rely on the interaction with scientists outside the Agency.

The Office of Cell, Tissue and Gene Therapies, the Acting Director is Dr. Phil Noguchi, who will be speaking to you shortly. Joyce Frye [ph] is the Acting Deputy. And the structure really deals with three primary divisions: the Division of Cellular and Gene Therapies, the Division of Human Tissues and the Division of Clinical Evaluation and Pharm/Tox.

I would just say while Phil was--at the time this slide was made the Director, Dr. Raj Puri, has been selected as the Acting Director. Raj is here. Where are you, Raj? Oh, there he is, right over there. And you'll see him. Dr. Ruth Solomon, who is the Division of Human Tissues, and Ruth's group will be continuing her work on the safety of banked human tissues, and certainly will continue as those areas expand, and a new Division of Clinical Evaluation, Pharmacology and Toxicology. Recently Phil has selected a new Acting Director for this, Dr. Cynthia Rask, who is--is Cynthia here? I don't see Cynthia, but we'll make sure she gets--she's doing the work. That's good. Somebody's got to be doing the work.

So under the Division of Cell and Gene Therapy, there's a cell therapy branch, a gene therapy branch, a lab of molecular immunology and virology, a lab of tumor

biology. Many of our cellular products are used as therapeutic vaccines. A lab or immunology and developmental biology and a lab or stem cell biology.

All of these things, obviously have great importance in terms of not only looking at therapies, but certainly in coordination with novel vaccine protocols.

The Division of Pharm/Tox, again, Dr. Cynthia Rask, who's now in the upper box. And we're going to be recruiting for a person for Clinical Evaluation Branch. And we are very close to selecting new leadership on an acting basis for the Pharm/Tox Branch.

And then I just wanted to mention the Division of Human Tissues, and Dr. Ruth Solomon.

I'm going to stop my formal presentation at the moment, to just talk about the interrelationship of cellular therapies, and also the proposed reorganization of having the therapeutic products from CBER be considered moved to CDER. I have expressed to certainly Dr. Crawford and Dr. Lumpkin the concerns that I the Center Director, and certainly the staff at CBER have regarding this particular transition.

We believe that the therapeutic products that we are talking about currently in this transfer, which include cytokines, growth factors, monoclonal antibodies, and a number of enzymes, as well as other related products, have important public health benefit. And I

really think that the science behind these and the scientific issues with these products are not all solved. And the need for having a research reviewer base model to deal with these issues continues to be important.

There is also a link in a relationship between these products and the ability of our new office to function. Many of the components in cell tissues and gene therapies require cytokines, growth factors, and monoclonal antibodies in order to propagate and use these new products. So in essence they are integrally linked.

When we had designed our new office, our office was designed so that these two offices were going to coordinate very closely within the Center for Biologics. That is, the clinical review, the review teams from our scientists in Dr. Rosenberg's group, which is therapeutic proteins, Dr. Webber's group, which is monoclonal antibody, to really support this as a whole program. We feel that it is a problem.

We also feel that many of our scientists under this scenario will leave the agency, and this is of grave concern to FDA beyond just the scope of the function of the new office.

I will not go into all the reasons. I want to link the predominant reasons to the new office that I'm here to discuss today. Dr. Crawford and I are in discussions on this, and will be further about the impact

of this on the FDA as a whole. And I certainly wanted to make the Science Board aware of this. This is a very important issue, not only to the products we currently regulate in the Center for Biologics including the therapeutic proteins, but also the future of how we're going to deal with these new evolutions of new products.

So I'm going to stop here. I would like to introduce Dr. Phil Noguchi, who will come and discuss some of the specifics of the new office, and then I'd be happy to come back and answer any questions you might have. Thank you.

DR. NOGUCHI: Yes, thank you. I'm used to using a touch pad, so I didn't notice there was a mouse here.

Thank you very much. It is my distinct privilege to able to present to you today and give you both a personal view of what I see the office doing. But I can assure you that this personal view is just a slight variation of what you will find throughout the agency at every level. The reason I call it a simple complexity in an evolving world is literally my professional life has been at the Center for Biologics.

I was actually started as a medical student when I was part of the NIH, and the next year I came back to continue some of my research, and was told that we were part of the FDA. And not knowing anything at that time, I hardly noticed the change. But my boss then was Dr.

John Petrucianni, and from John is really the philosophy of how we do business at FDA, and especially at Biologics. And as my own personal, kind of, this is about all I know how to do.

When I first started, John looked at me, and he said, "Well, let's see, you're young medical student. What's the problem, what's the issue, and what are you going to do about it?" And that basically is the same theory I've taken throughout the years and that we will continue to do throughout this particularly complex, or simplicity, or thus complex.

There will be three topics. I'm going to touch briefly on our counter-terrorism activities and show you how actually that weaves together directly into the function of the new office. I'll describe that, when we talk leveraging, I call it 'federal stone soup.' I mean we have enough to be able to create the regulatory framework, and create the regulations and the approval process, but we need everybody's help to contribute to this soup, so can finally have something that's useful at the end of the day.

And then finally I want to talk about patient-centered therapies. This sounds almost like individual tailored therapies, but it really is a little bit different. As I get to that, it's really that this society should be able to meet the needs of just one

person who have the rarest genetic disease or other type of disease on earth. We have the capacity, we have the wherewithal, we have the approval mechanisms. All we need is the will to do that.

First of all, some of the efforts in counter-terrorism: Whether you're a victim of terrorism, whether it's physical, chemical, or biological, or you're a victim of disease or injury, you're going to need things that repair, replace, restore, and regenerate normal body functions, and that's partly what we do. For example, with the era of human tissues, we've had some rules on the books since 1993. Last year, we believe that there are 600 to 800 thousand tissue transplants, musculoskeletal transplants, that have been done.

With the increasing numbers of transplants being done, obviously there also comes the need to have a closer oversight over that, but in a way that does not impede the currently vastly usable supply that we have. We will be finalizing the rules for our tissue framework, which will in fact go beyond infectious disease control and will introduce some of the concepts Dr. Crawford has for the reinvention of good manufacturing practices. We call it good tissue practices. This will emphasize record keeping, tracking, and donors' eligibility rules, all within the context of infectious disease control.

Hematopoietic stem cell transplantation has gone on for quite a number of years and is certainly now being considered to be the standard of medicine in many places. Radiation so-called dirty bombs, as one example we know from Chernoble that were the technology better available to be able to delivery hematopoietic stem cells in a timely fashion, perhaps there would not be nearly as many tragedies at Chernoble as there was.

So we're actually taking a slightly different modified approach to this, because we do want to mobilize this industry, both for its medical needs for standard transplantation as well as for the future. We're reviewing data that has been submitted by a number of our partners out there in the academic center. We believe we have at least enough to begin to start to do what we called "deemed licensing," that is, in lieu of a formal premarket demonstration of safety and effectiveness and the attendant lengthy times for that, we do believe that some of this area can actually be done in a somewhat retrospective manner, but without sacrificing anything in terms of safety and effectiveness. We're not nearly done with this, but we will be bringing back our current efforts in this area, probably in the next several months, the beginning of next year.

When we say "deemed license" we will to make sure, of course, that in fact, even though we deem it and

we don't have a formal premarket approval mechanism for it, that it does, in fact, talk about a safe and effective product. We have heard about other stem cells now.

Again for terrorism, counter-terrorism, some of the effects are really not known in the immediate sense. Anthrax has an immediate kind of a sequela, even though by the time you get the full-blown disease, the anthrax bacillus is simply nowhere to be found. There may be longer-term consequences from that, such as neurologic damage, pancreatic damage, or other tissue damage. We have been doing a lot in the area of embryonic stem cells and adult stem cells that are similar to these. We've held an FDA public workshop on that.

In your materials that I've passed out today, we're very proud that in the original primer for embryonic stem cell research, there is a Chapter 10, called the safety net for how you develop these things. This was authored by actually Donald Fink of the FDA, one of our staff members. And in fact when the report first came out, the first part of it that was leaked was actually Chapter 10, that is, how are we actually going to use this in the clinic. These are all the steps that need to take place.

We are going to continue to work on that and to work with the National Institutes of Health. We with the

NIH have been meeting with the approval stem cell providers, both from a scientific basis as well as from a regulatory basis. It's been extraordinarily fruitful to make sure that the FDA and NIH are not only at the same table but we're asking the same questions, that in fact the NIH is realizing quite dramatically that they need to fund those types of studies that need to be done, so that we can have safe and effective products for something that we don't quite know how to do yet.

Even tumor vaccines. Now, tumor vaccines as a theoretic entity have been around for 30, 40, 50 years. We have one sponsor, Dr. Don Morton, who's been in it personally for 40 years, and we see some progress in it. If we can get Don Morgan to finally admit that "Well, of course you have to make these products under GMP quality" and he built his own facility for that and has now transferred that to the Cancer 'Vax' sponsorship, we think that this is coming to fruition.

Well, what does this have to do with counter-terrorism? Well, one of the long-term sequelae of a dirty bomb, and what we saw in Nagasaki and Tokyo, is obviously development of all sorts of malignancies. Perhaps one area of use for this would be in the area of tumor vaccines, both for the need of the public at large and for the need of the victims of terrorism. We are having an international workshop in 2003 to follow on a

workshop we had earlier and we're beginning to start a partnership with industry to now start to get down to the real nitty-gritty issues. What exactly are going to be the release criteria? What exactly do you mean by 'potency' if in fact this is a tumor vaccine, but it's individualized, an autologous tumor vaccine?

This is what i described as federal stone soup. When we started about ten years ago in the area of gene therapies, gene therapy was then really quite new, and as the INDs were being submitted, every single one we put on clinical hold because they didn't have such things as, oh, like their clinical plan was, how they manufactured the virus and the vectors, simple things that we decided that we could teach each one of the sponsors and go through on an individual basis: "Well, here's your IND, these are all the questions you have to need."

But we think it's a far better way to actually first teach our own reviewers what do they need to look for. We'll be starting to release a series of what we call 'reviewer templates,' which are for our internal use, but will be for public dissemination and discussion. With these templates, these are all the things that we've learned over the last 11 years about what to look for, being put down in a document. We have our reviewers look at this, look to see whether or not they're in the submission. There are links to all the regulations, to

the ICH guidelines, to our current policies and practices. They're updated as we go along.

And by the way, we feel that within three to six months we can take a naive reviewer, and that reviewer can then generate about a 15-20 page review that's comprehensive. It's not excessive. We can identify the immediate issues to be developed at the IND stage, and will obviously be a good template for how we create the pathway for these and other kinds of products.

We are thinking, as a matter of fact, that these templates are so useful to use, we know that industry is going to be very interested in looking at these, so they know what kind of questions we're going to be asking. And these are not simple questions. This is not a fact of "Oh follow this and you'll get an IND and an approval." Some of these you're to have to spend perhaps literally millions of dollars to build the technology to address the question, but if that's what it takes to get something on the market, we already know industry is not looking for the easy path. And academia is not looking for the easy path. You're looking for the path that will give you products that will be patient-centered and that will lasting and can be developed for the future.

In terms of partnerships and federal stone soup, speaking of Jesse Gelsinger's death in late 1999, the NIH had a very large three-day meeting about it, and one of

the recommendations is "create a reference material standard for adenovirus, so we can compare our cross-trials." We have trials for cancer. We have trials for genetic diseases. We have trials that are just marking studies. A whole variety of things. But the infectivity one trial may use is different from another, is different from another, is different from another. This is an old concept of "create the standards so people at least can include that in their development, and we can now complete does 10-to-the-7th infectious units in the cancer trial equal 10-to-the-7th infectious units in the gene therapy trials for ornithine transcarbamylase.

With an interruption from 9-11, about two years ago, we put together a proposal. It was handled by the Williamsburg Bioprocessing Foundation. We set up a system which is quite remarkable. We actually called for bids for portions of what needed to be done, and the idea was you can bid for producing GMP quality material. You would bid for being one or more of the testing facilities to do the standardization for infectivity. You can bid for the testing for infectious disease and adventitious agent. Now the other part of it is "and you will volunteer everything for that." This is all pro bono.

We estimate that the material cost for this very large effort was something on the order of $750,000. However, the man hours that were involved from at least

40 different institutions--both large, small, academic centers, was clearly somewhere in the low to probably high millions of just man effort. An absolute prime example of what we should term federal stone soup: we provide the framework, we provide the ball park. You know, "Build the park and I know you will come."

We are also working with the NIH Stem Cell Task Force. This has just been initiated by Dr. Zirhoni, and that goal of that particular task force is "Well, you know they have all cell lines available, but there really haven't been very many applications for that. So the task force is to identify what are the impediments and they want to make sure FDA is there so that they can make sure that the studies that are being done will contribute to their present and future needs for any future cell therapies that use stem cells.

And finally to get to the concept of a patient-centered therapy. This is not individualized therapy. This is not taking pharmacogenomic measurements and trying to exclude patients based on a particular phenotype or genotype. This is really trying to say that "What if you turn the whole pharmaceutical development process on its head? That is, when you do a large clinical trial at Amgen, as an example, although you are looking for a patient population, you identify that up front, by and large it's "If you take this, it will

work." Of course, it doesn't fit any one person exactly well, but for the average, for the bulk done during a clinical trial, it works not too badly.

We think we--everyone, you all--can do better. This is where the patient defines the therapy. The patient walks in the door, may need a knee replacement, needs a new mechanical device, and at the same time has psoriasis with another treatment. And so forth and so on. This means that we're turning everything upside down. We're talking about market share, because everybody needs to play in this. The large pharmaceutical manufacturers absolutely must be a part of this. It is only they who have the large capacity to produce the reagents, to produce the cytokines, to produce the monoclonal antibodies, that are necessary for patient-centered therapies.

So it's a share, it's a niche. It is not dominance for the market. The delivery is obviously evolving. If we're going to do a gene therapy, where do you go for that? Can you go anywhere in the country? The answer is 'no.' Somewhat facetiously I give the example of "We need thinking like, well, you can go anywhere in the world and get a McDonald's hamburger, and you may not like it very much, but you know it's going to be same. You know it's going to not cause you food

poisoning." Whereas Jack-n-the-Box, they couldn't even do that very basic thing of quality control.

So there are opportunities for delivery for the infrastructure that needs to be built. A part of it is we also need to get the first patient therapy approved. Obviously, financing product developments are evolving. But most of all, I'd like to propose that for this process, the patients who are out there, who have missed the opportunities of biotechnology are the ones to drive this process. It doesn't matter how pure the insulin is, if you are a brittle diabetic, you still feel lousy, you still are not controlled. You may die from your diabetes, and not necessarily from the diabetes. Very often these patients just pass out right while they're driving a car. My stepfather almost did the same thing, as a brittle diabetic.

Now, do we have any examples. We think we have at one prototype example of a patient-centered therapy. There is a syndrome called "X-Link Severe Combined Immunodeficiency Syndrome." X-Link because it's on the X-chromosome. The popular term is "bubble baby syndrome." This is a lack of a gamma C chain, which is a part of what makes up receptors for cytokines. This particular gamma C--actually without having it you loose five different cytokine receptors, and so you have essentially no T-cell function. You have relatively

normal relatively normal but not adequate B-cell function. There is a death within the first year of life if it's untreated, from severe recurrent infections.

If you could get a full HLA identical transplant, usually from the sib, you can get greater than a 90 percent survival. Unfortunately only about 20 percent of the time do you have such a person available. Haplo-identical transplant becomes the second level of transplantation. It still carries between a 50 to 30 percent mortality rate. And in both of those cases, the reconstitution that you see is adequate; that is, you can survive, you can do pretty well. But we don't know about the long-term survival very much. The oldest is now 19. And usually the patients at the minimum need monthly or quarterly infusions of gammaglobulin because their B-cells, while somewhat normal, really are not adequate for typical antibody responses.

Now, it's not without its own hazard. In France, nine of 11 children showed evidence of immune reconstitution following gene therapy. Just late this August, actually right at Labor Day, one successfully treated child out of the nine that were treated in France developed a leukemia-like syndrome.

We had a quickly constitutive BRMAC meeting, or Biologics Response Modifier Advisory meeting, on October 10, 2002, and in a way it was really quite remarkable.

Because as science put it, "What do you do when you have when you have a successful treatment and the risk is really unknown but it's there?" The significant findings was that in fact, the gene insertion by gene therapy that led to the therapeutic effect also caused the leukemia-like disease. As Stu Orkin put it, more succinctly, if you see an animal with four legs and it has stripes, you call it a zebra. If you see a child with leukemia and it's got a gene therapy and a retrovirus has inserted in an oncogene associated with leukemia, you tend to call it leukemia. So the clear risk at an unknown frequency is that the same therapeutic event can cause a disease. The child has been treated, however, not in complete remission, but is still surviving at this time. Obviously we are looking at it very closely.

Because of this potential superior immune reconstitution, these kids actually do well for both their T-cells and their B-cells. And ironically this one young child actually developed chicken pox and was able to withstand that and actually to throw off the chicken pox somewhere probably after the malignant event occurred. But clearly immune function restoration is quite large in these individuals.

We are going to make sure that the trials that will start in the United States--we have two for X-SCID, will have all this information available. There will be

new test requirements for looking for clonal expansion, and within any child that is treated, and a whole bunch of other things that are related to that.

We will also be going back and making sure all the informed consent process for all retroviral gene therapies are done. And that is a process, in fact Dr. Cynthia Rask is right in the middle of heading that project up.

Let me just illustrate to you what we're talking about here. It's very simple to say, "Well, we had a gene therapy and we got a cure." Here we're talking about exactly what was done in France and what will be done in the United States in several trials, trying to replicate that experience. The end product is on the right-hand side the CD34 putative stem cells--probably not the stem cell, but within that population are the primordial stem cells--that is now expressing the normal gamma C receptor. That is the product, per se. You notice that the Office of Cellular Tissue and Gene Therapies does not have the word, "product" in it, because this product, we lose count. You start with cord blood, you pass it over an FDA-regulated column that has FDA-regulated antibodies into a dish that's FDA-regulated because it's a flask. You take a murine retroviral vector, which is an FDA-regulated product, into a fibronectin, oh that's another FDA-regulated product

flask, to do your transduction, in which you add three or four growth factors that by themselves have yet to show clinical benefit to patients, but in combination are critically important for the ability of the retroviral vector to actually transduce those cells and lead to a therapeutic effect.

With apologies to Dr. Davis, three out of the four are now at Amgen. Stem cell factor Flit 3 ligan [ph], and IL-3. The pegylated MDF is a different product. Just to divert just a little bit, there are issues in terms that are still available because Amgen owns the intellectual property for three out of these four. And clearly they do want to make sure that their products can be used and developed, but they don't want to lose the intellectual advantage, nor do they want to be in a position where if something goes wrong, they get blamed for that.

Well, we're working with Amgen and with the National Cancer Institute to work out an arrangement whereby in fact we can start to address those kinds of things. The issue right where is that as an entity, this particular patient-centered therapy, it is unlikely that any pharmaceutical company wants to do the whole thing. On the other hand, clearly if we start thinking about market niche, if we have stem cell factor that is clinical GMP quality, from a licensed manufacturer, why

would we prefer that over getting something repackaged by Sigma? And that's part of the issue of where we are going, part of the types of issues that we will be facing.

I put this in a little bit of a tabular form, here, to just say there are about five different areas, each of which overlap because, for example, we have devices, but the devices have monoclonal antibodies. We're looking for surface markers. Some of those devices have extracellular matrix whose regulatory status, per se, may be a little bit confused, but in this context, are part of that whole cellular therapy.

Specified products, or these recombinant products, stem cell factor Flit-3 ligan--in no way does the fact that they're used in small quantities in an ex-vivo situation mitigate the fact that they need to be in their own right as safe and as pure as possible. We feel that the pharmaceutical biotech industry is a place where that can be done on a reasonable basis, and must be done. The quality of each part of the products that go into the final therapy here, we cannot compromise on the quality. And that quality simply comes from the coordinated review, the coordinated review of the science, the coordinated review of the research reviewers, that can make that happen.

If you look at all this, and I am not going to spend a lot in terms of what the proposed transfer of products will do, but let me put it to you in a very practical way. It is a little bit daunting, and I was much more comfortable just a few weeks ago to launch a new office that actually is smaller than most divisions at FDA. Because I knew I had the support of OTRR. I had the support of the Center Director. We could do this, we could work it out.

Transfer of the scientists, of the products, of the expertise, no matter how you cut it--some will be lost, some will want to go, very likely not too many. Some will leave. Some will go to other centers. Some will enter private industry because we train the very best. Our folks can go out any time they want, and they know it, but they don't want to. They want to do the right thing, which is this.

We need that expertise for the medical review. We need that expertise for the products. I need to know for sure that a CD34 monocloncal antibody actually has undergone the same type of review that we have for a therapeutic monoclonal antibody. And you know what? Sometimes that slips through the crack. And you know what? If it's not within our Center, it's going to be extraordinarily hard to necessarily figure out where it's going to be don. In our Center, we are a product-

oriented center, so in one sense we try to package the whole review of the product, the clinical Pharm/Tox review, the compliance, and everything else. Although they are in different offices, we are one center that does it. If it goes instead to a medical indication, so Flit-3 Ligan may go to several different divisions because of the medical indication, it will be impossible to adequately address the issues for a therapy, a patient-centered therapy such as this.

We think that the reasons for it--we don't know what the reasons for it really are. But in fact I can tell you that for the new office to function, it's a bit of a bite. And I'll leave it at that.

But no matter how hard this may be, at the end of the day the question is "Is it all worth it?" and we say "yes." Learning the lessons of the past absolutely enables a future, and what can be imagined will be done. And as we move forward we always do this with hope, because we always hope next year it'll be a little bit better. We know for those X-SCID babies, even the parents who know that one of them may develop leukemia, they want to take that risk. We need to have appropriate humility. Far too often as we move forward, we kind of forget just basic things.

Originally 1902 Law for Biologics was because people kind of forget. Horses get sick too. A horse

named Jim came down with tetanus before it was discovered. That was to create a diphtheria antitoxin. The diphtheria antitoxin was a wonderful therapeutic agent, but its use was being discredited because of that.

The 1938 Food, Drug, and Cosmetic Act. I don't know how many men, women, and children died because sulfonylmide was insoluble in water, so what did they use? They used antifreeze. They didn't even try it in animals first.

We need to remember that nature's been everywhere, she's done everything. And if it doesn't exist, there's a good reason why. And when we perturb that system, we need to tread with due caution with humility and not hubris. This is progess. The race is not to the swift or the battle to the strong, but as everybody in a manufacturing facility knows, time and chance happens to us all. And most of all, as we move forward, we need to move forward with compassion.

Thank you for your kind attention, and Dr. Zoon and I will be pleased to take any questions.

DR. LANGER: Thanks. So, we'll open it up to questions. Harold, why don't you go first?

DR. DAVIS: I actually have--the CBER/CDER reorganization, but I'm not sure if this is the time we want to do that in an open discussion, et cetera. I'm not sure how you--

DR. LANGER: I think that probably the best time to go over anything is now, unless people want to break things up, but it seems to me now we should go over any of the topics that Kathy or Bill raised.

DR. DAVIS: I guess I was a little confused about the fact that--procedures for recruiting somebody and then calling--recruiting. Are these internal recruits--are you recruiting--

DR. ZOON: Most of the recruits--when you establish a new office it takes time to write all the position descriptions and formally advertise them. So in order to implement a new office what we do is do an advertisement for a detail, which is an acting position. All those position descriptions can be written and then formally advertised. This is a method that helps the program get started and up and running, and clearly it's important to do that and get people--in this, but sometimes that could take anywhere from six months to a year to get all those position descriptions written, classified, and advertised and ultimately filled. We need to do this in order to get the operation up and running.

DR. DAVIS: --the child who came down with leukemia, how long post treatment--

DR. NOGUCHI: We don't know the exact date of the actual--there was a development of--we don't know,

but it was at least two and a half to three years after the initial treatment.

DR. DAVIS: I guess my comment, and this comment ought to be taken from Harold as opposed from Amgen. In the time I've been on the panel, I don't think anything we've discussed as a science board, potentially--like the proposed--and I'm not --even good or bad, just the fact that it could potentially impact that. So I'm very surprised that the Science Advisory Board--considering being brought in to offer an opinion on that, or to view that, et cetera. If we are to review the issues around the science of the FDA, to me nothing we've looked at since I've been here potentially has an--impact like that. I was actually very happy to hear Dr. Crawford--say some members of the board or subcommittee or something would be set up. My concern around that is--did that come from--. Did BoB, did you and somebody else propose that? If that's an FDA thing--

DR. LANGER: Yes, I think I'll have to ask Lester about that. I don't know the answers to that. I think all of us probably want to do whatever we can to help in any way. So, probably what could happen on this is get a sense of how different members of the board feel and, you know, we could make some recommendations to Les. I'm not sure what else we can do. I mean I'm open to anything, myself. Yes?

DR. ROSENBERG: I also would like to comment. I spent yesterday, I just spent the afternoon, very enjoyable afternoon, listening to the science programs at CBER, and perhaps that combined with the fact that I've also had fifteen years of interaction with that organization from my prior experience in the pharmaceutical--and when Kathy was talking about this research or review model, what came across yesterday loud and clear was how important that model is and how well it works for the type of review they do, in terms of novel biological materials, and how integrated that process is and how it requires this kind of interrelationship, to be able to have the cutting-edge science in place to be able to look at those kinds of novel products.

And the case that was just explained, of course, is just one in terms of how therapeutic modalities intermix with cell tissue and gene therapy. I think it's even much more complex than that. I think there's interactions between adjuvants and vaccines, and the same cytokines that are being used therapeutically are being considered as adjuvants.

The whole process of what they do is so integrated, and it's integrated right from the point of view of helping companies to develop these things, in providing feedback to those companies, that assistance. Also in approving them and getting the right approval

capabilities. And then regulating them, particularly regulating them from the manufacturing standpoint, and all the again kind of unique properties of these kinds of molecules and the science base it takes to monitor that.

So given that kind of background, I would like to certain support what Harold just said, and that we just heard about all this week. And given the importance of that science base to the ability to give feedback to the industry, to regulate this industry, to approve products in this industry, to monitor manufacturing processes across the divisions that were discussed--I really am very concerned that we do not disrupt that science, that we make sure that whatever gets done--and again, I don't enough about this to know the reasons for or against moving things, but I think before you move something, somebody's got to present a very logical and rational reason for doing that. And I certainly haven't heard that. As a member of the Science Board, nobody's presented that. It's never come up for discussion. And I'd like to hear more about why this is going on and where it came from and what its purpose it, because I know that its potential effect sounds like it could be pretty traumatic. And therefore, we'd like to know and help out if we can to do something.

DR. LANGER: I don't know if there are any comments from the FDA, or whether we should just--Les is

not here--or whether we should just continue with comments from members of the Science Board, or questions.

Okay, Bob?

DR. NEREM: Several comments. Number one, this is not something that just happened. It's been in the news for at least a month, if not longer. But it was my understanding that in fact Lumpkin was going to give some background on that, and then unfortunately had to go down to the White House, or whatever. But certainly it is something that probably deserves further discussion, but it's unfortunate in a way that this has come up the way it has, without hearing first what the rationale of upper management is, and it's difficult for me to know to be pro or con, as probably most of the Science Board members. But I do think it's important.

Here, one of the things, which at least my understanding from Dr. Crawford was that this subcommittee talking was not to look at this specific issue, but to look in a broader way at the organization of the FDA, and certainly I would support the FDA thinking out of the box, in terms of how they should be organized with the products of the 21st Century. And I consider it a very positive thing. Because I would assume that a subcommittee would meet before the next board meeting and at least produce some homework. So I viewed that comment by Dr. Crawford as a very positive

comment, but not something that was meant to address this particular issue, which doesn't mean that it shouldn't be addressed by some group.

I don't if Kathy--now, I like to come back to this office, and I would gather that you're probably not ready, you and David Feigal, to talk about some of your ideas, and you'd rather wait on that. Is that fair?

DR. ZOON: Yes, but I think in terms of conceptually, I think the discussions we have are going to very much reflect how we think. We can work together in a seamless fashion to deal with these products in a step-wise, risk-driven strategy, where the amount of oversight and regulation is coincident with the products and the issues surrounding the products, and that we do this in a way that is mindful of both the scientific underpinnings from both centers to make sure that we're coordinated timely and working in teams.

And so I won't go into more details 'til we work out the specifics, but I think much of the philosophy and the needs of this particular tissue engineering field have been heard loud and clear, and we're trying very hard to incorporate those ideas into the concepts of furthering the science in this area and to make sure that the centers do it in a coordinated fashion.

So right now we have our teams working very hard on this issue and coming up with a strategy. We will be

presenting that to Dr. Crawford and others, and hopefully they will be pleased with what we come up with, or provide feedback that we can go back and work on. So my sense is there should a positive solution.

DR. NEREM: Just a couple of comments. You know, one of your slides--I think it was your slide--was expertise, and that list of expertise was actually striking in terms of what you have and equally striking in terms of what you don't have in terms of what you don't have when it comes to tissue engineering products, and that's why it's so important that there be a cooperative effort. And I would hope that in thinking out of the box, you would even be considering the possibility of a joint office that is jointly staffed. Having gone through the CDRH review a year ago, the idea of calling in consultants doesn't seem to be the optimum situation. You need people who are working side by side on a day-by-day basis, and that are helping to educate each other as to the problems that come from the different sides.

DR. ZOON: I totally agree with you, Bob. I think that we recognize that each of the centers has some very precious expertise. It does not serve either center well to duplicate expertise, but to coordinate and bring teams together that have responsibilities. And so that is what we are trying to achieve in our planning and our

strategies to work together on these new products. And I think that teamwork and dedicated teamwork will be a reflection of the concepts that we are putting together.

DR. NEREM: The other thing I would suggest is that one probably should not be talking about a device approval process versus a biologics approval process, but sort of starting from scratch, what is the right approval process for these complex products. And I don't know whether a different process would require legislation, but if it requires legislation, so be it, because we need the right process, not some shoe-horning products into an existing process.

DR. ZOON: Yes, I think there's a way to approach this. And particularly because the centers have the opportunity to use all of our legislative authorities and regulatory schemes, we actually have a lot of flexibility on how to manage these products. And so my view is that we should give it a go, and use what the tools are we have to make it the very best we can. If after an evaluation, because I think it's important not only to act but to evaluate what you do and how effective it is. But to implement something, look at its effectiveness, talk to the people in the field, and then see is this effective.

And then once we can do that, we can do an iterative process as to how this should be best moved

forward. But we have to start somewhere within the given tools, and I would say this field needs to move forward and not get tied up in knots. And then we can work together with the patients, with the industry, with the academic institutions to move it forward.

DR. DAVIS: Thanks, Bob, for clarifying that around the subcommittee. That's actually quite helpful.

But two points. One, I still believe if we're going to attack an issue or deal with an issue with the subcommittee, what I've seen to date with us is that the agency brings an issue to us they'd like for us to consider or wrestle with, and then this committee has sort of decided how to deal with it--to put a subcommittee together, et cetera, et cetera. So that doesn't allay all my concerns about the fact that there will be future subcommittees.

And you also made a point which I agree with. In the last few years we've actually reviewed issues around various individual centers, and I can't understand how we would deal with individual center issues around how they're structured. We've looked at the retention issues, the seniority issues, hiring people, where do you find people, et cetera--how those issues were any more scientific oriented for this Board than the potential issue around what's going to happen if we should merge CBER into CDER. And please understand, I'm not speaking

for it or against it at all. It's just the fact that if the agency is going to that, I would say that my friends who would hold up and see that FDA has a science board, advisory board, and that my name is on that science board, would probably have assumed from a public standpoint that that was discussed at this board.

And we are very far along, there's a quick time to turn this whole thing around, et cetera, and I'm not sure of what the board can say or do or what will be discussed and what impact we can have, et cetera, and that concerns me.

DR. LANGER: Other comments or questions?

Yes?

DR. SCHWETZ: I can't speak for Dr. Crawford or Dr. Lumpkin, but in the absence of both of them--I know you're going to leave today--unless we have an opportunity to discuss this with Dr. Crawford yet today, which I don't have reason to believe is going to happen--I would predict you're going to go home with a feeling of nonclosure on this. And while I can't close it for Dr. Crawford, let me just say that you've made some very good points and I appreciate your effort to make this a generic issue as opposed to a very specific one, and I think your recommendations are good.

I would suggest a couple of ways that we might help to bring some closure to this, even if it isn't

today, to do it in the near future. And that is--I think I can speak for Norris. Norris and I will relay the nature of the comments to Lester immediately, as soon as we can meet with him to share your concerns, because of the time lines of what is going on, that we don;t want to go in and talk to him after the fact.

So we will talk to him and relay the thoughts that you have put forward.

I would also volunteer that you might personally call him. There isn't reason by Science Board members can't call the acting commissioner and share off-line thoughts, raise questions, interact with the person to whom you are the advisor, outside of meetings. So I would encourage any one of you to ether speak on your own behalf or you and your fellow board members to the extent that you want to relay the discussion that went on here, and your concerns, and the discussion that went on yesterday over at CBER. I think it would be appropriate for you to share your feelings with him by telephone or by whatever means you would like.

Thank you. Norris?

DR. ALDERSON: I agree with what Bernard just said. Bob just gave me a draft of something that I think he's going to pose to the board to relay to Dr. Crawford. And I think that's very appropriate that you do that. I think he's captured here in a statement your concerns

that I hear you saying. And I think the point that Bern made about this is not specific to this issue, but it's more of a generic issue which you are addressing, and I think that's the way you need to do it.

DR. LANGER: I want to see if there are comments from the audience. Anybody want to make any comments from the FDA or elsewhere around the table? Okay, sure.

MS. ROSENBERG: I'm Amy Rosenberg, and I'm the Director of the Division of Therapeutic Proteins in CEBR in the Office of Therapeutics. And I would like to make a comment that echos some of what I've heard around this table. And basically that is that we feel that this consolidation plan was formulated in the complete absence of what is regarded by the scientific community as critical input. That is, input from authorities responsible for oversight of FDA scientific programs. The Science Board to the FDA, the Biologic Response Modifiers Advisory Committee, or other subcommittees appointed through these committees.

The plan to move much of OTRR's research programs into CEDR contradicts recommendations previously made by a subcommittee of this Science Board that drafted a report finalized in October of 1998. It's now known as the Bennett Report. And in his report, the committee resoundingly reported the requirement of a high-quality intramural research program for regulation of biological

products, including biological therapeutics, and the committee stated that "It is the consensus of the committee that CEBR requires a strong laboratory research focus and not a virtual science review process. Otherwise we risk the potential to damage not only the health of the population of the United States, but also the health of our economy."

They further stated in no uncertain terms that the culture of science, which is so strong at CEBR and necessary to the regulation of biological products, is specifically absent from other centers. In so stating, the committee stated that the review committee in expressing its strong support of the need of laboratory research in CEBR and other centers in FDA, recognizes that this position is contrary to the experience of the agency and the industry in the review and approval of drugs by the Center for Drug Evaluation and Research.

So among the many critical reasons that the committee offered in support of CEBR's and OTRR's intramural laboratory research programs were the following: one, regulators and policy makers require expert knowledge and firsthand experience with the latest technology being applied to biological products. And I think a group of you yesterday saw a presentation that highlighted the cutting edge proteomics, genomics, and other programs that we have at CEBR, and the fact that

our scientists stay there. We have very low turnover. They stay there because they love what they do. They love they love the integration of science and regulation. And they're dedicated to it. These people could make much more money if they went elsewhere. But they're dedicated to this. But they're dedicated to it because the science is incredibly satisfying, as you all well know, and they're not going to go to a center wherein research will not be supported.

Secondly, the committee stated that an intramural research program is required to assess risks of new therapies, to develop assays and new approaches to increased efficacy, safety, and reduced risks.

The third comment was that a strong well-maintained intramural research program provides the basis for a climate of science and scientific communication within CEBR that enhances the ability of the agency to recruit and retain high-quality scientific staff. And in that light I would ask you to consider the presentations yesterday and also the bibliography that we passed out this morning of publications from the Office of Therapeutics. I believe that this shows that we have an outstanding publication record, and it's remarkably done so while over 50 percent of the time of these research reviewers is spent in regulatory responsibilities.

Furthermore I would highlight that the proposed consolidation poses a real threat to retention of the high quality scientific expertise. Recently we conducted an anonymous questionnaire of OTRR personnel, and found that about 90 percent of principal investigators and tenure track fellows, and staff fellows, will seek alternative employment if the consolidation plan goes forth as planned.

Fourth, the research program facilitates the ability of CEBR to address existing regulatory issues and anticipate future problems, to keep pace with rapidly emerging and complex cutting edge technology. And I have already alluded to the cutting edge science that we have at CEBR, which may not stay, should it be placed in an office where science is not supported and there's not a critical mass of scientists.

With regard to existing regulatory issues, we interact extensively with industry. We've organized many, many meetings to address what for biological therapeutics are critical issues, that of immunogenecity, comparability, and the prospect of generic biologics.

So in summarizing, because the conclusions of this report are so clear with regard to the requirement for research, we feel that the input of the Science Board to the FDA to this consolidation plan is of vital importance, and notably has been absent.

And we welcome your comments, we welcome further input of the Science Board, and really very much encourage your participation. Thank you.

DR. DAVIS: The questionnaire that you said was done? How many people are we talking about? How many people were sampled? You said 90 percent of the people responded one way or the other? Are we talking about ten people, 100 people?

MS. ROSENBERG: We're talking about, I believe it is 100, at least that we've so far gotten questionnaires back from. But the majority of persons are within DTP and DMA.

DR. DAVIS: That's 100 out of 140? 100 out of 300, or...

MS. ROSENBERG: Do we have the numbers? Dr. Max can speak to this.

DR. MAX: I believe there are approximately 140 to 150 people within OTRR. We had a response from about 86, so it's not complete. We don't know if it's representative, but that's what we got. We tried to assemble this so we could give you some idea at this meeting. We carried this out earlier this week and it was primarily in response to comments that Dr. Crawford had made, suggesting that the attrition rate that we could expect and that he's seen so far since the

consolidation was announced was no greater than the normal attrition rate at the FDA.

Of course, it's only been announced for one month, and to allow people to seek alternate employment as professionals, we wouldn't expect to see any change in the attrition rate, even if they did have the intention of doing so.

DR. DAVIS: So the 90 percent is 90 percent of the 86?

MS. ROSENBERG: Yes.

DR. LANGER: Other questions or comments by anybody?

Thank you very much. Any other comments from anyone in the audience? Or the FDA?

I think that a number of good suggestions were made about how we can all individually collectively follow up. But I think probably it's also important to have something on the record for sort of capturing briefly what has been said here today. So I've made an attempt at that, based on Marty's and Harold's comments, and I wanted to just read that and then let people modify it, so that we could somehow capture the spirit of this briefly. So here's what I will say on the proposed move of therapeutic products from CBER to CDER. The board is concerned that the science not get disrupted and wants to better understand the reason for this move. I tried to

just make it--that's actually taking a number of things that you said, but I just want to try to put something down that captures this in some way, and I just want that we can put it in at the end of the day.

Again, I want to open this up, so if anybody wants to modify that or just say it's fine. What do you think?

[No response.]

DR. LANGER: If there's nothing else at this point, we'll take a break for lunch, and we'll resume at 1 p.m. for the Open Public Comment.

[Whereupon, at 11:37 a.m., the proceedings were adjourned, to reconvene at 1:03 p.m., the same day.]

A F T E R N O O N S E S S I O N

1:03 p.m.

DR. LANGER: We'll get started with the 1 o'clock session, where there's Open Public Comment. So I just wanted to check to see if anyone from the public would like to make comments. Do we have any comments?

[No response.]

DR. LANGER: There is one written comment that's been submitted by a Dr. Kathryn Stein. Dr. Stein was unable to be here to present these comments, so I'd like to give these to the transcriber to incorporate them into the official transcripts and dockets for the meeting. This letter covers the proposed CDER/CBER move that we discussed earlier this morning. So let me give that.

[The statement of Dr. Kathryn Stein follows.]

DR. LANGER: Just in case anyone did walk in, are there any other, any public comments that anyone wants to make before we close this particular session?

[No response.]

DR. LANGER: So I'm checking with my colleagues about what we're going to do next. We're moving so quickly. Let me get the advice of my colleagues at the FDA, unless someone would like to tell some jokes.

DR. SCHWETZ: I don't tell jokes well, so I don't attempt to, but I would like to raise something serious that we might talk about in the few minutes before they arrive, and it is to take advantage of the transition in chairs and to have some discussion, either some thoughts from yourself or discussion from the board, on how we might do a better job of Science Board meetings, of keeping the Science Board members informed, while identifying issues to bring to the Science Board, how we might operate, whatever details you might like to raise.

And, Mike, as you look at filling this chair, there are things that aren't necessarily fixed in concrete in how this happens, and we would welcome some new thoughts. We'd welcome recommendations from people who have been on this for a long time and have obviously seen how we work. Bob, any thoughts on how we could do this better?

DR. LANGER: I think we can always do better, and really the only way is doing exactly what you said, just getting advice from people on the Board, at the FDA and from people here. I have no particular ideas. I do think, and we'll talk about this later in the day, you know, further defining the precise role of the Science Board is an important thing to all of us, and so I think that's something we discussed in the morning and at lunch a little bit more, and we'll go over that in one of the written statements at the end, but I think it's really just getting feedback from people to see how we can do it the best possible way.

Whatever we've tried to do the last few years has been based on, you know, what I've heard from different people, both at the FDA and on the Board. So I think it's just continuing to get feedback from everybody here. I don't have any specifics. I know we're going to be in great hands.

DR. DOYLE: Well, I think we have been in great hands for four years, so there's some big shoes to fill here.

But I guess one major question I have is how do we go about identifying agenda items for the Board, and I know many or not all of the agenda items come from the FDA, and are you receptive to having more input from

Board members in terms of identifying agenda items and, if so, how do we go about that?

DR. SCHWETZ: Absolutely. We are interested in items that you would like to have on the agenda. We haven't had meetings between meetings, where you might have that as an agenda item to talk about what do you want to have in the next formal meeting, but, Norris, I think we should come up with some kind of a mechanism whereby we solicit comments, maybe halfway between meetings, a couple months after the meeting to get some ideas and then pass the agenda for the next meeting, maybe more than just in front of the Chair. We could pass it by in a draft form to the other members.

DR. ALDERSON: I'm personally open to anything you want to do relative to the agenda. The only thing I would tell you, it takes a while to put the program together, in terms of scheduling staff, so we need to start, you want to do this, tell me how you want to do it, Chairperson. So I'm perfectly open to any input you want to have on this.

DR. DOYLE: I think we'll have to talk about that as a group and get back to you.

DR. ALDERSON: Okay. That's good. It could be in the form of a conference call, for instance, and we could set that up or you could come with a number of list of proposals. You could give us some things that you'd

like to see, and we can determine whether they're doable or not.

DR. DOYLE: And another point that has been discussed among the group is the idea of what Dr. Crawford had brought up about a subcommittee of the Science Board to address how the FDA might be reorganized, and the sense that I have from my conversations with the group is that they'd rather have everybody be invited, and some may be too busy, but they'd rather have it an entire Board activity, instead of just a subcommittee, if that would be acceptable.

DR. DAVIS: I guess my point, along that line, I think there might be times where a subcommittee is very appropriate to dig into something, get the ball rolling, bring it back to the Board, et cetera. I just think the Board ought to be, it ought to be up to the purview of the Board how to attack an issue on behalf of the Board, but I could see times when a subcommittee might be useful.

DR. SCHWETZ: I would remind you that in the past we have also used members of the Board of Scientific Counselors to be part of a larger subcommittee, that we would bring together with specific expertise to deal with a question, whether it was review of a center or the Korn report kind of thing or if we wanted to have a group of people, when you think of the IOM reviewing the structure

of NIH, I would hate to be in your shoes as a member of the Science Board and be assigned the task of reviewing the structure of the FDA. That could be a huge task.

On the other hand, if there are parts of this that you would like to take on, it sure would be helpful, even if it meant just getting your opinions without doing a huge amount of homework on it would be valuable.

DR. DOYLE: Another question that comes to mind is the issue of obesity, which is a big issue today as we read in the paper, and it would be interesting to know what FDA is doing in regard to this public health issue.

DR. SCHWETZ: This is an issue that I have personally taken up as one that I want to, and being in this position of being the ex-acting Commissioner, I'm fortunate to have time to be able to devote to this issue. So I have been working within the Agency to raise the level of attention to nutrition and overnutrition, and obesity, and what other things might be all a part of that package.

So I agree, Mike, that that would be a great topic for discussion. I would like, I would suggest that if we do talk about that, we might expand it in the broader picture of the public health service, and maybe it would be appropriate to have somebody there from CDC, who is very actively engaged, I mean, they have people who are very heavily engaged in obesity as a problem.

We could have somebody from the Surgeon General's Office, we could have somebody from various Institutes of NIH, and if we want to explore how the FDA could be doing more in the context of the Department structure on obesity, that might be a fruitful discussion, as opposed to the brief discussion of saying that, in reality, the FDA is doing some, but not a huge amount. That's the status today.

DR. DOYLE: Does anyone else have any thoughts?

[No response.]

DR. LANGER: Thank you. Great. Okay. We'll get started then.

So the next topic is Pregnancy Labeling/Research & Study Design on Medications Used by Pregnant Women, and Susan Wood is going to lead that, and we'll also have Margaret Miller and Kathleen Uhl speak as well.

Susan?

DR. WOOD: Thank you. Go ahead and have Peggy come up, and when Kathleen Uhl gets here, we'll--

[Interruption to fix microphone.]

DR. WOOD: We'll slightly reorder the presentation today, but we want to talk to you about a number of the activities focused on pregnancy and medication use by pregnant women and what we do and don't know about it, and what we do and don't regulate about it.

So we're going to talk about a couple of different areas throughout the presentation. First, I'm going to briefly do an overview of the Office of Women's Health, and I think a number of you are familiar with this already, what we've been doing around clinical trials in women, and what the problem really is, in a nutshell, around addressing issues of pregnancy and medication use during pregnancy.

If Dr. Uhl is here, we will then move on to discuss revising the pregnancy labeling. If she's not, we'll save that part till the end and move into the research activities, which Dr. Miller will speak about, and then we'll talk to you about some of the issues that we have regarding pregnancy labeling, research, information about medication use and ask your input on where we, as an agency, we, as the Office of Women's Health, need to be going and what are some strategies that we can take on and adopt to try and tackle some of these complicated questions because we know these are both not trivial, and there are no simple answers as well.

The Office of Women's Health is part of the Office of the Commissioner, and we focus no a wide variety of activities in women's health, serving as a champion for women's health, both inside and outside the Agency.

Our activities range from funding a number of research products, including the specific area of pregnancy research, but others as well. We also have an outreach campaign this year focusing on diabetes in women and their families, and we also then get involved in regulatory and policy issues. Again, the pregnancy rule and regulatory activities is a prime example of that type of activity that we're involved in across the Agency involving multiple centers.

As you all know, the clinical trials approval process, we're asking questions about products being safe and effective. We ask for data on proper doses, and we want to know about adverse effects. I think when you take these questions and apply them to pregnant women, we often find that the information is lacking and does lead to questions about are we dosing pregnant women properly to effectively treat whatever the condition is and are we really getting information on adverse effects, both for the mother and for the infant.

In 1993, and continuing through to the present, we work under a guideline on studying gender differences in the clinical evaluation of drugs, and we encourage the participation of women in clinical trials, although it is not required, in terms of numbers per trial. We call for the collection and analysis of data looking for gender differences, and we recommend that there are

methodologies that can be used to minimize risk of fetal exposure by eliminating pregnant women from studies through design of the studies at all phases.

But, in fact, that eliminating of pregnant women, although done for very clear and understandable reasons, leaves us with a problem. When we come to looking at pregnant women as patients, pregnant women with health conditions that do require treatment and that how, as more and more effective treatments come on the market, how do really treat, and advise, and label products for use during pregnancy when we know women are taking them?

The problem, as stated on the slide, is that pregnant women are healthy, and I think we know that chronic conditions, in particular, ranging from hypertension, asthma, epilepsy, diabetes, these all require treatment, and women who have these diseases get pregnant and pregnant women have these diseases. So we have to work on these conditions and recognize that medications are taken.

There's also a belief that pregnant women should avoid taking prescription drugs at all, even if they do have conditions that require it, or only use older medications with good safety profiles. That may be sort of where we are, as a reality of where we are, but there is also a reality that some of those older medications

may not be as effective, and they may have more adverse events than newer products on the market, not necessarily the ones that have just come on the market yesterday, but ones that are several years old and we have experience with, as opposed to 20-year-old products.

But the fact is, as I mentioned earlier, many pregnant women do need prescription products to maintain their health and to maintain the pregnancy, but these products are not tested in pregnant women, and pregnant women are actively excluded from clinical trials.

What we're going to talk about today is not only the labeling information and what is and is not available and how useful is the information on a label regarding use during pregnancy, but how to go about ethically, safely, and usefully do studies on pregnant women who are taking medications to begin to get the information on the appropriate dosing and efficacy of these products during the various stages of pregnancy and postpartum.

That sort of is laying the groundwork of where we're going to talk about today to lay out this problem, and ultimately we want to ask you questions about how to prioritize our efforts, how do we encourage more research in industry and academia, because FDA is limited, and then what other strategies are out there to actually collect data and other information on drugs that are used by pregnant women.

We'll circle back around to those questions at the end of the presentation, but because of, again, the range of topics and the complexity of some of the questions, we're going to try to go through both the labeling issues in some of the research that we're doing.

And right on cue. So you didn't hear my introduction, Cook, but that's okay. She knows exactly what I said.

So, again, these are the issues for the Board that we're going to be looking at, prioritization, how do we facilitate research and what are some other approaches and strategies.

At this point, I will turn it over to Dr. Cook Uhl, who is a medical officer at CDER. What's the official title?

DR. UHL: Pregnancy Labeling Task Force.

DR. WOOD: Pregnancy Labeling Task Force.

DR. UHL: Thanks, Susan.

Good afternoon. Thank you for the opportunity to speak. What I'm going to do is go through kind of where we are now with the Agency with respect to labeling for pregnancy and lactation, where we are, why we're there, and what we're trying to do. I have about five slides with which to tell you that.

So, currently, in the CFR, the regulations addressed pregnancy labeling in 1979. Prior to that,

there was nothing that was required in labeling about pregnancy. The intent of that legislation or that regulation was to assist health care providers when prescribing for women who are already pregnant.

It does not address anything regarding inadvertent exposures. What do we mean by inadvertent exposures? We mean a woman who is pregnant, doesn't know that she's pregnant and is taking a medication and then finds out that she is pregnant.

Why is that a concern? In the United States, 50 percent of the pregnancies are unexpected. That means they're either mistimed or unwanted. As far as numbers go, there are 6 million pregnancies in the U.S. per year and women of reproductive ages of 15 go 45, 10 percent of those women in the United States become pregnant annually. So it's a pretty significant problem about unexpected exposures or unintended exposures in pregnancy.

The current category system focuses specifically on teratogenic risk, and it uses letter categories. I'm briefly going to walk you through what the current pregnancy letter categories are.

The categories are A, B, C, D, and X. A is when there are controlled clinical studies in humans, and A is used very rarely. There are about five products of which currently have a Category A.

Pregnancy Category is B is when the human data are reassuring, but there have been positive findings in animals or the animal studies show that there's no risk.

Pregnancy Category C is a conglomeration, basically, and the majority of our products are labeled as Category C. More than two-thirds of our products are Pregnancy Category C. A Pregnancy Category C can come about when there are no human data, there are no animal studies or the animal studies show some findings. Animal studies are positive.

Pregnancy Category D is when human data show risk, and there's a concern here about benefit outweighing the risk. For example, some of the products that are used for seizure disorder, some of the anticonvulsant medications, where a woman has to be taking this medication for controls of her seizures. However, we know there's a teratogenic risk. Some of those compounds are labeled as D.

Now X is when there are either positive animal or positive human. Another interpretation of X, though, is that these products are contraindicated for use in pregnancy or these are drugs that should not be used during pregnancy.

Now let me give you an example of that. Oral contraceptive products. Oral contraceptive products are obviously not intended for use during pregnancy. They

are intended to take to prevent pregnancy. Because they are not intended for use in pregnancy, they have been given a Pregnancy Category X designation.

So, needless to say, there are limitations in our current system. The current pregnancy categories are overly simplistic. The A, B, C, D, X is oftentimes felt to represent a linear continuum of risk, meaning A is better than B, B is better than C, C is better than D, and so on.

From a clinical standpoint, this type of labeling is not very helpful, and it's not very informative. The categories combine different levels of risk assessment. For example, that's the Category C. You could have a Category C because the animal data are positive or because there are no human data.

The current system also combines risk information with benefit, and that's specifically seen in the D and the X. Currently, most of the products have only animal data, and by nature of the way that the studies in animals are done, the findings in animals are commonly positive, and with that a lot of the products then are Pregnancy Category C.

At the current time, there is no requirement or incentive to update these labels with human experience. From the pharmaceuticals standpoint, as well as from the medical-legal standpoint, oftentimes, warnings in

labeling are perceived as optimal. It's felt that it's better to just warn don't take these if you're pregnant. Unfortunately, because of that, it's very rare that these labels will be updated with human experience.

Now, despite that or probably because of that, there are changes coming to the Agency. There are changes coming to the current pregnancy labeling, and that's predominantly what my job is. That's what I work on, but what we are working on, there we go, is to have a label that provides clinically useful information and information that's useful to the patient, as well as the physician or other health care provider when making a decision about prescribing drugs in pregnancy or prescribing decisions that had been made prior to pregnancy and pregnancy has occurred.

So what we're in the process of doing is working on revising the regulations. Now the current physician labeling rule addresses pregnancy and lactation as a special population. However, that portion of the labeling rule does not provide the information that should go into that. So we view this as a regulation that just provides the content and format for pregnancy labeling.

What this does, first and foremost, is to get rid of the pregnancy category designation. The intent is to separate out information about risk from information

about benefit, and this will use a standardized descriptive text that characterizes risk, has built-in flexibility, but it is not a simple letter categorization.

In addition, this will separate out animal data from human data and risk that's ascertained based on animal or human.

Also, the labeling will distinguish what says here is clinical advice, but actually considerations that should be given in the clinical setting for prescribing in pregnancy or for discussions of inadvertent exposures, and it will separate out that type of information from fetal risk information.

In addition, the label will address the inadvertent exposure, and it will address--it will address it by providing information about dose, duration of exposure or the gestational timing of exposure for which you would be most concerned for fetal risk.

Because there are numerous physiologic changes that occur in pregnancy, the point has been raised about whether the dose that's provided in labeling for an otherwise healthy male is an appropriate dose to give to pregnant women. So information about optimal dosing will be provided, and this will include whether there are any pharmacokinetic or pharmacodynamic changes that occur

during pregnancy; in addition, any information about unique maternal adverse events.

Lastly, because the risk information requires looking at all data that are available, there will be a requirement to update the label and to provide clinically relevant information in the label.

With that said, Dr. Margaret Miller, from the Office of Women's Health, will now address some other issues.

DR. MILLER: So as Kathleen said, as we were working through this reformatting exercise, it became clear that having good information to put in the label was going to be critical to improving the health of pregnant women and to helping prescribers make accurate prescribing decisions for the pregnant women.

So what I'd like to do now is talk about some of our efforts that we've been engaged in over the last two years to try and improve the content of information that would go into a label, and in embarking on a discussion about research and pregnant women, I think it's important to mention the ethical concerns and the ethical rules that we have to comply with.

The basic regulations for conducting research in human subjects for federally funded research are contained in 45 CFR Part 46. They are subpart (a), which are the regulations that cover protections for all human

subjects. And when you're doing research on pregnant women, you also have to comply with what's known as subpart (b) of those regulations.

Now, under the basic protections or subpart (a), if a product or a study represents minimal risk for the patients or the participants, you would be able to get an expedited review through the IRB. However, when you're doing studies in pregnant women, they are considered vulnerable subjects, and so all studies involving pregnant women have to comply with all of the full IRB approval requirements.

In addition to complying with all of the requirements under subpart (a), when you're doing studies in pregnant women, you also have to comply with subpart (b). Now the regulations under subpart (b) changed about a year ago, December of last year. We have a new regulation under subpart (b). Let me just briefly talk about the new regulation. I'm not going to go into the changes for this group.

First of all, if you are a pregnant woman, you can give informed consent and engage in research if the research that is being conducted has already been conducted on animals or nonpregnant women. So that we have information about the safety of the product in animals or nonpregnant women.

DR. DAVIS: Those are pregnant animals?

DR. MILLER: It does not say pregnant animals. It says appropriate studies. So there's some flexibility about what is the appropriate study in animals, but it has to be appropriate studies in animals. One would assume they'd be reproductive type of studies.

If the research is designed to meet the health needs of the mother, so we're doing the study to meet the health needs of the mother, and the risk to the fetus is minimal or the minimum that can be achieved under the studies, then the woman's consent alone is sufficient.

Also, if the research is designed to meet the health needs of the mother, the mother and the infant or provide general knowledge that would help us in treating other pregnant women in the future, then the consent of the mother is sufficient for her to participate in the study.

If, however, the research is solely for the benefit of the fetus, you're enrolling pregnant women, but you're really not worried about the woman at all, you're looking at the benefit to the fetus, then to enroll those women in the study, you need to have informed consent by both the mother and the father before the woman can participate in the trial.

Now, as we've mentioned a couple of times, pregnancy, for those of us that did it kind of remember this, it's a time of dramatic changes. You end up having

these changes I think for the next 25 years, but I'm still recovering.

[Laughter.]

DR. MILLER: You have this huge fluid volume issue. Your heart rate goes way up. Your urine output just goes through the roof, and then there's all these metabolic changes in the liver that help you do this remarkable event.

And all of these changes or some of these changes or maybe these changes, these dramatic physiological changes, have an effect on how a drug is distributed and metabolized in the woman during pregnancy, but as we've mentioned already in this talk, really we have very little information on what the pharmacokinetic and pharmacodynamic changes are because for most drugs that has not been established. And so clinicians are relying on information from nonpregnant women, we hope, but in many cases it may be healthy male subjects that those studies were done in.

So some of my partners in crime over in Drugs thought that perhaps we could make a dent in this problem if we were to conduct some studies on pregnant women and work through the protocols of how you would go about doing these studies if they were to be done, and so we put out a solicitation with the Department's Centers of Excellence on Women's Health. These are 14 academic

institutions that are one-stop shopping in women's health. They have research, clinical services, education, both of professionals and outreach component.

And we wrote for them a statement of work and asked them if they could do a PK/PD measurements on pregnant women that were currently receiving prescription medication to treat a chronic condition that they had during the pregnancy. The idea was that we would take these women that were currently undergoing therapy for some chronic condition, and at discrete periods during that gestation, collect PK and PD information from them.

We thought that this would serve as a prototype for how we could collect needed dosing information in both an ethical and hopefully economical way. It is our intention, as Kathleen told you, we have a place in the label where you could put this type of information in the proposed new labeling. So this would be the type of information that could be incorporated into the pregnancy label.

So, as a result of that solicitation, we funded, in fiscal year '01, two studies. The first is kind of a traditional PK study, in which we have a cohort of about 20 women that have hypertension, and they're receiving Atenolol to treat their hypertension, and we have recruited them into the study during the second trimester.

During a window during the second trimester, they undergo intense blood sampling, so that we can determine the PK characteristics during that period. They do a similar thing during the third trimester and then in the postpartum period.

The second study is what's known as a population PK design, and what this does is this gathers up a lot of--Cook is laughing because this is so different from you're used to. You take a whole population of pregnant women that are receiving Labetalol for control of hypertension and you do spar sampling. What you do is you use this large number of people to draw your population pharmacokinetic variables. So they don't have to be during a certain window, they don't have to be off of concomitant medications. They could be lactating/nonlactating, because you're drawing the kinetics over the whole population of pregnancy during the whole time.

So we have one of each of these different designs that we're funding in the hopes that then we can see how these would, if we were to write guidance, how do you work through issues? Have we thought of all of the different issues that need to be thought of in designing these studies because now we've lived through it.

So this year what happened, and probably you've already had a briefing on bioterrorism, but with the

anthrax scare, it became very clear that we did not have dosing and safety information for many, many of the products that were going to be used to treat infections that could occur as a result of bioterrorism in special populations.

Most of the studies that are done on those medications were done in the military, and the military does not intend to have a high percentage of pregnant and lactating women or elderly. So our database of information on those populations was severely lacking.

And so to address this issue, we once again thought that we could do some studies in the pregnant and lactating women, and we set out two different solicitations. The first was to try and collect some safety information to assess both maternal effects and infant outcomes in pregnant women that were exposed to medication during pregnancy, and these were medications that we might want to use to treat women exposed to a bioterrorist agent.

And it's our thinking, at the Office of Women's Health, that if there's a fetal safety concern, if you're worried that this drug might harm the fetus, the likelihood that you're going to give that medication to a pregnant woman is probably diminished. So it's not going to be a case where you're sure she's had an exposure to anthrax; it's going to be the case where we're not sure,

and we're going to want to prophylax, and it's going to really influence your decision of whether or not to provide prophylactics to a woman during pregnancy.

So we were interested to see if we could use these large automated databases and the diagnostic codes to try and get some information on infant outcomes.

And the second solicitation was very much like what we had already done with the antihypertensives, where we would ask for PK/PD studies to be conducted in special populations.

So the study that we funded under the safety studies, although we asked for both fetal safety and maternal effects, the databases that were available and the solicitations that came in only were available to address fetal safety. So we are only looking at infant outcomes.

The study that we've contracted to do is with Vanderbilt University. It's going to look at infant outcomes and Ciprofloxacin, Doxycycline, Amoxicillin and Azithromycin. And you can see the number of pregnant women that were exposed to those medications in their database there.

In addition, we've asked them to do a control group, and this is pregnant women that were exposed to an ACE inhibitor during their pregnancy, and we wanted to include this group because we wanted to make sure that if

women were exposed to a product that we know causes birth defects or adverse infant outcomes, that the databases that we use will be able to pick that up. Because, remember, these were prescription databases and treatment databases. They weren't databases designed to look at safety. So we have included pregnant women exposed to ACE inhibitors as a validation group or a positive control group.

We also have a group of women that were pregnant and exposed to no antibiotics, and the study includes a group of women that were exposed to Erythromycin. These investigators have already investigated Erythromycin in their database and shown that there is no increase in adverse infant outcomes. Women are exposed to that drug during pregnancy.

We are looking at infant outcomes at birth, three months and a year to see whether you pick up more teratogenic effects if you go longer, and the patient population that's in this database, it's the Tennessee Medicaid database.

The projects that we're doing with the Centers of Excellence, the dosing projects are very similar to the ones that we did in '01. We asked for PK/PD studies in pregnant and lactating women, and we also asked that they collect information on infant outcomes if they're

doing the study in pregnant women, and we asked for the elderly.

Now we've funded four projects under that, but I'm just going to talk about the two that are having to do with pregnancy. The first is a PK study on Amoxicillin in pregnant women. This drug is excreted renally, and so we think that dosage adjustment may be needed in pregnancy.

The second contract is actually quite interesting because the University of Wisconsin is going to conform a consortium of five different Centers of Excellence in Women's Health, and they needed to form this consortium because in order to get enough women exposed to these drugs while they're pregnant, we couldn't just go to one site. They're not being used because of fetal safety concerns.

So we have a consortium of five different COEs that are going to try and address Ciprofloxacin, Azithromycin, and GENT.

Just one last point, the CDER has recently put a guidance on how to conduct a pregnancy registry. That is on CDER's website, and one of the things that we learned, as we were talking to the women's health community is, while CDER has issued guidances, actually, required pregnancy registries for a number of products, that the women's health community was not aware of this activity.

And just to let you know that a pregnancy registry is a very effective wy of collecting safety information on marketed products, and you enroll pregnant women after they've been exposed to a drug, but before the birth outcome is known so that we can see what is the effect of the drug on fetal outcomes by enrolling women in the registry.

So what our office did is we came up with a pregnancy registry website, and the point of this website is to tell women about registries, explain to them what they are in as simple terms as we could come up with, and then tell them how to participate in registries. And we have provided on the website a list of all of the registries that are currently enrolling women that comport with CDER's guidance. So, if someone is conducting a registry, but it's not conducted the way CDER would like a registry to conduct it, we're not including it on this website.

So that is all I have, so I'll turn it back to Susan.

DR. WOOD: To round all of this up, I think, in talking about the labeling issues, which all of these steps are sort of in process, the labeling changes are still very much in process and will require a lot further input from not only the rest of the Agency and the Department, but also then obviously, you know, input from

the practice community and the women's health community about whether the proposed changes are what ultimately will become the rule from FDA.

The research projects, again, are just taken on to sort of break, you know, break through the barriers, the beginning barriers on doing this kind of work. We are very aware that the Agency and the Office of Women's Health or any other parts of the agency are not going to be funding drug-by-drug, study-by-study to collect the information on products both currently on the market, but products coming onto the market, but rather we want to be able to develop a model system, work through what the issues are and what the problems are, and then develop a guidance on how to carry out this research by others, others who have a vested interest in this.

I think there's a real question that if we have products that are out there on the market that we know are being used by pregnant women, and we know that we don't have the information on how to properly dose and treat women with either chronic or acute conditions with medications, there is sort of an ethical question, you know, is it ethical to not do the research.

We have a number of issues that we have to make sure we handle doing studies on pregnant women very carefully, and with the highest scrutiny, and to make sure we're doing it in the safest way possible, but at

the same time, we know there are women out there taking drugs every day, and they're pregnant, and they need to be taking them, but we don't have the data to support appropriate clinical care, and if a woman requires an antibiotic, but is underdosed and then needs to take a different product, another course, or a second course of the same product, we're not minimizing risk here, we're actually mistreating both the women and potentially the offspring. So that's sort of our motivation with trying to start this, but it leaves us with remaining questions.

Peggy also talked about the outreach to women themselves, and I think using the web page and by talking about these activities, we're starting that process, but there's a long way to go with a lot of this information. I don't think we want to be telling women too loudly that we really don't have the information on how to treat them, but we do--but I think it does behoove us to start collecting the information and making that information available in a label as soon as we can.

So here are our discussion issues. Did we want to hand out?

DR. MILLER: I did.

DR. WOOD: Okay. Did you hand out the little flyer too? We also have just a summary sheet, which is not exactly up-to-date. The counterterrorism studies are still listed as future activities, but sort of summarizes

as a take-home of some of the activities that both we and CDER are doing in the area of pregnancy.

But these are our discussion issues for the Board, which is given the complexity of this problem, how should we prioritize this effort, in terms of either identifying products to study, focusing in different methodologies and so on.

How should we encourage others to take up this research on pregnant women to help, again, break down those barriers and the very natural hesitancy to take on this work?

And then are there any other strategies that would be effective, other than these direct intervention-type studies for obtaining information on drugs used by pregnant women?

I'll ask my colleagues to come back. But these are our thoughts on sort of where, and you've gotten this sort of very quickly all of the complexities, but if there are any other--

DR. LANGER: That's great. Do you want to ask questions or give her the answers?

[Laughter.]

DR. RIVIERE: [Off microphone.] [Inaudible.]

[All microphones are now off.]

DR. MILLER: There was no question. He has a comment. He's commenting on my question.

DR. RIVIERE: [Off microphone.] I think the population pharmacokinetic strategy is probably the most effective way to leverage the research because some of this [inaudible], and it's just not excluded for various things. They're excluded for very good reasons, but as the whole database gets built up, collecting a little bit of information in the pregnant population knowing the disposition for the rest of the population, we can learn a lot.

So, anyway, I encourage that. That's more effective than some of the most classic approaches.

DR. WOOD: Peggy, did you or Cook want to comment on how well that design is working or how it was received by the statisticians and so on?

DR. MILLER: [Off microphone.] I, too, liked, well, I didn't like it. I found it very difficult to figure out the population pharmacokinetics. I struggled with that for a very long time. We are not having as much success recruiting the large number of women that we need in that trial.

The traditional design has full patient recruitment, and we're basically just following them through, and the other trial has lagged behind because we have so many more women that we're trying to recruit into that trial. So the challenge there is finding the larger numbers of women, and that's why, with the COEs, that's a

completely population approach, the five consortiums is taking the population PK approach across the different centers.

DR. RIVIERE: Because the advantage of the population approach is you will also pick up other co-variants and other concomitant variables, and you can leverage the nominal population into detecting that. So, again, I would just encourage that's the direction it's harder to get patients, but when you do have the full study developed, you'll get a lot more information out of it.

DR. UHL: I appreciate your comments. One of the interesting things though that we had was the IRB. The fortunate thing for the population PK was that we had a statistician on the IRB who had a very good understanding about Bayesian theory and hence made that very simple.

For people who don't have a kinetic background, first of all, clinicians don't have a kinetic background to begin with. So when you start talking kinetics, it's very difficult to simplify that to the clinician level to the bedside, and how we take population PK data then and do that will be very challenging because of the same thing.

A lot of kineticists have a difficult time with population PK, but from an enrollment standpoint and also

in pregnancy, where you may not use therapy continuously throughout pregnancy, but you might want to dose differently throughout pregnancy, the population design helps very much.

DR. RIVIERE: I would think today most of your Phase 2 clinical trials and Phase 3 clinical trials use population in kinetics.

DR. UHL: Right.

DR. RIVIERE: Right. So there should be some expertise to leverage--

DR. UHL: Oh, yeah, I'm not talking about in the drug industry or in the Agency.

DR. RIVIERE: Right.

DR. UHL: I think that that expertise is there, but who uses the drug? The patients and the health care community, and population PK doesn't mean anything to them. I mean, what you need to do is translate that then into a recommendation for dosing appropriately.

DR. RIVIERE: To get that information, the best route is, seems to be, population kinetic--

DR. UHL: Well, we'll see. We're looking forward to what we get out of this.

DR. LANGER: Do other people want to make comments or would you like to just kind of go down the list and--yes?

DR. DAVIS: I've got a question, and I hesitate to ask it, it's out of naivete. I would assume where is the big problem, and you kept talking about prescription drugs, which I think I understand, but I had this picture of all of these pregnant women out there taking over-the-counter drugs that we have no idea about what's going on, et cetera, and I'd just assume more pregnant women are taking OTCs than they are prescription drugs, even, and so we have no idea what it's doing or--

DR. WOOD: I think that's a very valid question, and someone may have an answer to in terms of actual prevalence, but I think our concern with prescription drugs is that we're talking about medications that women need to the level that they've gone to their health care provider, and they're under care, and they need prescription drugs.

I think the culture and the prevailing belief, even though it may not be acted upon in reality, is that women minimize, pregnant women minimize drug use of any kind, over-the-counter or otherwise, throughout pregnancy in order to avoid a bad fetal outcome.

Whether that, in practice, I agree, I mean people are maybe taking their OTCs by the handful still and laying off their prescription meds, which actually we'd probably prefer the reverse, that if they'd lay off

the OTCs and only take what they really need to be taking for a direct health condition.

Did you have--

DR. UHL: I can maybe comment a little bit on the prevalence of use in pregnancy. There are several studies that have been reported in Europe about drug use. It's easier to get to that data in those type of health care systems, and what's been reported is approximately three to five prescription drug products are used per woman during her pregnancy, and that excludes prenatal vitamins and iron, as well as some over-the-counter.

In our country, it's hard to get to that type of information about the prevalence of use. The most recent study published in the U.S. was almost 10 years ago, and it confirmed what's been seen in some of the European countries, but it's about three to five drugs per pregnancy, and the number of drugs increases with increasing complexity of the pregnancy and increasing maternal age.

But your issue about OTCs is well-founded, as well as other things that we don't like to talk about, like dietary supplements and such, because people think that those are safe.

DR. LANGER: Other questions at this point or would you like us to try to go down that list or what would be most useful?

DR. WOOD: Sure. I mean, we can just start with the first question. I mean, in terms of priority, I mean, priority can be interpreted to be priority of how do we prioritize products that we should be evaluating, how do we prioritize whether going at some of these research questions versus some of the other approaches, that would be our first question.

Any thoughts or comments?

DR. DAVIS: If you look at--if you believe the data there is three to five drugs on the average, they must fall out into perhaps some kind of category of drugs. So one of the things I was thinking, you could make a decision around the prevalence of drug types, and then use representatives of those categories.

On the other hand, you could decide that certain categories of drugs are much more likely to have effect based on what you already know about them, and prioritize that way.

DR. WOOD: Yes, I think that--and, unfortunately, sort of the cross-hatch of that is probably then most drugs. You know, that most drugs fall into one of those two categories.

There is an effort referred to as the Safe Motherhood Campaigns that have been going on reflecting a variety both of elements within the nation, you know, from the public sector to the private sector to advocacy

and so on, focused on how to promote safe motherhood and healthy pregnancies.

A piece of that is trying to get at this priority--at women taking medications, because they're the ones who are at highest risk for not having a healthy pregnancy. And a piece of that is looking at trying to pass legislation calling on FDA to work with NIH to set up a prioritization of products along those lines in terms of prevalence or highest risk and developing a priority listing of drugs, highly dependent on, I think, NIH to then carry out some of the research that's necessary.

But that is a pie-in-the-sky kind of thing right now and is not really moving forward in terms of a mandate for the agency to do that. So I think within the agency now there is interest in doing that kind of thing, but lacking of the resources or the ability to bring in our colleagues at NIH to carry out some of that activity.

DR. ROSENBERG: Again, just a question mark. Obviously you've chosen antibiotics, I assume, for the reason that there must be a prevalent use of antibiotics among pregnant women? Do you have enough epidemiology to know which things you should be looking at?

DR. WOOD: Well, part of that--I mean, I think the antibiotics idea came from the counterterrorism and

sort of the list from, you know, what's going to be in the national stockpile and that sort of thing.

DR. ROSENBERG: How do you know what to study without knowing what they're most--

DR. WOOD: Part of that came from the proposals in terms of what they think is in their patient population, but--

DR. UHL: I'll be happy to address that. the Office of Counterterrorism and Pediatrics--am I saying that right? Something like that. Well, as CDER was undergoing a reorganization, we were located within that office, and the office director was given monies to study for the counterterrorism. And one of the aspects was special populations, and it was blatantly obvious this time last year when the whole anthrax scare happened that we did not have ample information to provide about dosing for the special populations, meaning pediatrics, geriatrics, and pregnancy. And it was very--you know, the recommendation from the CDC as to what were the drugs to use for prophylaxis for anthrax, there was not good information for what we should be doing for pregnant women.

So, given that, the monies were allocated for counterterrorism; in conjunction with that office we selected which would be the drugs that would be used in the event of some type of biological attack.

DR. WOOD: I think he's asking how do we know that there's actually a patient population taking it on a normal basis for care. And I think part of that came in from the proposals. They were able to say we have access to a patient population X. Not all the products that we identified were selected for study, and they were selected for study in part by the fact that there were patients available who were taking it for other reasons during--

DR. UHL: Right. And these centers were able to provide information to us as to how many patients they have had at their institutions, any pregnant women at their institutions treated with those drugs of interest.

DR. WOOD: In order to say they'd be able to do it again in the next year.

DR. SCHWETZ: As a result of anthrax, more than 30,000 people got some antimicrobial agent. Some of them must have been pregnant, and it's been more than nine months. Do we have the outcome of those pregnancies to do the study based on the data that we already have?

DR. MILLER: Pregnant women were not prophylaxed. I mean, the recommendation--I agree. Half of them got pregnant, and then CDC is collecting pregnancy outcomes if women were inadvertently exposed. But the decision was not to prophylax women that were pregnant.

DR. WOOD: So it would have been very early-term pregnancy.

DR. MILLER: Yes, so it would have been an inadvertent exposure, and we don't have the results of those yet. But it is being collected by CDC.

DR. DAVIS: Having some experience with the NTP where, in terms of choosing chemicals to study, you know, where they do bioassays, and there's never enough resources to study all the compounds, but there is a mechanism in place where different agencies make recommendations and somebody picks based on some criteria which compounds to do, sort of shooting from the hip I could see where various centers, based on some criteria--prescriptions written, toxic profiles, whatever--might want to make recommendations to a central group like yours to study compound X, class effects, representation of class members, et cetera, so that you could--because I don't think any way you do it you'll ever have enough resources to make a dent in terms of all of the compounds that are out there, obviously. There needs to be some rhyme or reason behind it.

DR. WOOD: Yes, I guess that actually segues into the second question about how do we--I mean, and after--I mean, I think that's a really interesting model because the NTP program--but it sits there with that mandate to do that, and with a pocket of money, although

not the world, but it works on a prioritized set. And if we were to get in that kind of place, you know, perhaps we could move forward. But at this stage, if we were to try and say at this point industry, whose products are the ones we're talking about, as well as academic centers who are interested in developing this kind of database systems, but are very hesitant about doing studies on pregnant women, I mean, I sat in a meeting not too long ago surrounded by a few clinical trialists and explained--and this is actually before we were about to award our first round. And they, you know, were shaking their heads and saying, well, I would never apply for that money. I mean, to the point where they say they wouldn't apply for money, that was sort of a shocker, you know. And that much less trying to spend their own money to do this in terms of industry.

DR. LANGER: Jim?

DR. RIVIERE: Following up on your earlier comment, everything seems to be looked on either on the infant outcome or the pregnancy outcome of the use of these antibiotics, which many of them are really relatively safe, generally. I guess the question would be: What about the treatment outcome, the efficacy? That's where I would see all the physiology totally--

DR. WOOD: That's what we were interested in, and we tried with the database method that Peggy

described, but we couldn't link--we knew we had the prescription use data for the mother and we had the infant outcome, but apparently the database had trouble getting long-term outcome health data on the mother as well as--

DR. RIVIERE: Well, even short-term outcome--

DR. WOOD: Even short--I don't think--they couldn't--they didn't have any good markers. I was really pushing for that as well. And there weren't any good maternal outcome markers that they could get out of this particular database, which is one of the better ones around.

In terms of the direct studies, I think the PK/PD studies that we're doing, I mean, I think that is our goal, is the PK/PD to some degree, you know, outcome--short-term outcome data for the mothers, how well are these antihypertensives working, how well is the antibiotics working. And we're getting some of that.

DR. RIVIERE: If you go back to the bioterrorism situation, what happens if pregnant women were exposed to anthrax? The important question, I mean, looking at these drugs, I wouldn't be concerned about ampicillin being a teratogen. The key is when you effectively get a dose of drug to prevent anything happening to the mother--

DR. WOOD: Well, I mean, I think that's our interest, and Peggy pointed out, though, even if there's a--if there's a hesitancy, even if there's some good outcome data on some of the products, or if there's some known risk to the product for an infant outcome, there may well be a hesitancy to dose the mother, particularly prophylactically, if you weren't sure. So that's our concern because if we don't have the data on how to dose her correctly, there's still the issue of will she get the dose at all.

DR. RIVIERE: I would think there's got to be some databases out there that link through--there's different databases on controlled--again, there's got to be databases that a pregnant woman is put on this drug and taken off that drug, there's a reason relative to response. That might get at this a lot faster.

DR. UHL: There are lots of problems, though, with the longitudinal databases, and the purpose of those databases are for billing. And to be able to extract information for epidemiologic purposes, although they're used, there are limitations to their use. And you would have to know what code you would be looking for for failed efficacy, and that's not usually coded. If a woman's being treated, say, for pneumonia and has failure to improve in 72 hours on this antibiotic and is switched to another one, the code would probably still say

pneumonia, and you'd have to capture the switch in therapies so that the clinical record has to be linked to pharmacy record as well. And there's a lot of problems with that.

Hence, our reason for using the PK/PD approach where we're not looking at efficacy in the pregnant woman, we're looking at similar--how can you get a similar kinetic profile at different stages of gestation because, from a PK/PD standpoint, that should translate into efficacy. As long as you know what PD parameter for the antimicrobial interest is the important one. Is it time above MIC? Is it an AUC to MIC? That type of thing. So we don't have to do an efficacy study to get to that. We can assume that if you have the appropriate dose that you'll have the same efficacy.

DR. ROSENBERG: Again, just a question. Is there anything you can do in the hospital setting that, again, because of risk/benefit and because of the controlled environment you could learn about certain things that might be relevant more generally by using a hospital setting where maybe more serious infection or pregnant women are now in a controlled situation where you're getting--you're constantly tapped into the bloodstream, draw as often as you want? Is there anything that could be done there that would help--

DR. WOOD: I think that's similar to some of--the antihypertensive studies, the women are in a very high-risk pregnancy situation.

DR. ROSENBERG: They're in the hospital setting--

DR. WOOD: Well, they're not in the hospital setting, but they're in a very--an outpatient clinic that specializes in high-risk pregnancy.

Do you want to comment?

DR. UHL: They're done like any other kinetic study is done. They're done in a clinical research unit. But if what you're saying is you think it would be easier to study, I mean, maybe--that's what I'm interpreting. It would be easier, potentially, to study pregnant women in the hospital setting.

The flip side to that would be you still have to get IRB approval, and that seems to be the biggest stumbling block. And would these women be potentially at higher risk than women with the same condition that didn't warrant that they were hospitalized? It's a huge can of worms. Could you more easily get the data that you want? Could you more easily get blood draws? Possibly. But you'd still have to go through the same administrative issues.

DR. WOOD: I think the point about the risk, if the woman is hospitalized for her health or for, you

know, potential miscarriage going on, you know, the likelihood of interest of participating in a clinical trial versus a PK/PD study is probably less than one who is at a high-risk pregnancy but not to the point where she's in the hospital and worrying about a crisis.

DR. ROSENBERG: No, I didn't mean that. I meant more in a hospital because she has pneumonia; therefore, you've got to treat her with antibiotic, irrespective of her pregnancy; therefore, you're going to get the data you want, not because she's in for another reason. She's in for the reason where the high risk makes you want to have to treat and, therefore, she's going to be treated anyway because it's her risk that's now forcing the treatment. Now the question is: Can you use that population to get the data?

DR. MILLER: Just to interject here, we are doing IV gent, and I believe all of those women, even in this day and age, will be hospitalized. Maybe with HMOs I guess I should--but they are going to be ill and they are going to be in the hospital, and they're going to be receiving IV gentamicin, and the consortium of COEs are going to be addressing that by getting five or ten women from each of the different sites in order to drive our population PK approach for that drug.

DR. DAVIS: I guess you have to be careful if you so focus the group to those who happen to be

available, because in the end, the question is: Is it gentamicin that you really want to know about, or does it--because it is a highly used one, or is it just because those patients who get on it are so sick and clearly use it anyway, so--but I think you have to define where you're trying to go with the data, or does it represent a group of drugs and so you're going to look at this as a class, because you're not going to be able to test every drug. So if you only test ten, do you test the ten you can get, or do those ten represent something or how you're going to interpret the results of those ten in light of all the other drugs? But if they're the top ten, you don't have to interpret in light of other drugs because they are the ones most commonly used and will stand on their own? And I'm not sure what the premise is.

DR. WOOD: I think we've taken it from a couple of--I mean, I think we've combined those. We're taking it from a couple of different strategies. The first time around we said we can find a few studies and we want to look at products that are commonly used in chronic conditions because we think those are a high-priority set of conditions. And based on the proposals we got, we ended up with the two antihypertensives that we're looking at.

With the counterterrorism thing, again, it was, you know, we have now a group and, you know, based on a priority setting of both the stockpile and what we think vulnerable populations might be exposed to or might need to be exposed to in a terrorist attack, and then, again, waited to see what was available, what's convenient within that group and what's doable--rather than what's convenient, maybe the word doable, and we sort of went that strategy. But there probably are other strategies. You know, we--and we could continue on and sort of dig down in those areas, or we could move on to other classes or priorities.

DR. LANGER: I had a question that relates more to the second than the first, but is there--and just my naivete. Has there been good research or significant research done on sort of trying to model, like say you understand the physical, chemical properties of a drug and you understand it's half-life, you know, so there's--say you know pharmacokinetics and biodistribution in a non-pregnant individual, could you--has there been any good modeling studies to say if you have that kind of information that you could then make even a reasonable prediction on a pregnant one?

DR. WOOD: I haven't heard of any. Have you?

DR. UHL: I don't believe so. To stretch that a little further, there has been a lot of discussion about,

for example, drugs into breast milk based on physical/chemical properties and such. And in that case, there's enough discussion about the differences of across animal species and animal milk that we're not sure how well they correlate.

As far as pregnancy is concerned, the changes are not static. They're very dynamic changes throughout the nine months of gestation that to model that would be very problematic.

DR. LANGER: I'm sure it would be very difficult, but, I mean, the question is--but I wonder if that's--I guess what I'm trying to get at, is that a direction of research that's worth pursuing? In other words, let's say you could encourage NIH to put out a request for proposal. I'm sort of thinking in answer to the second question, you get NIH to put out a request for proposals to try to do those kinds of models. It seems to me that that's something that pharmacokineticists or chemical engineers might be interested in doing if they were encouraged to do it. I guess the question would be whether it would be of any value to you.

DR. UHL: I'm not familiar with anything in the literature about doing modeling like that on the pregnancy side. There's a lot of information in the literature about physical/chemical modeling and PK/PD as far as lactation is concerned, but this would--to do some

pregnancies sounds to me like it would be creating a new field or--which is good, but with limited resources, where do you want to go with that?

DR. WOOD: I think your point about NIH--

DR. LANGER: But that's number two, not number one. I'm not suggesting that the FDA fund it, but what I'm thinking about is actually, you know,--

DR. WOOD: That might be less scary to people.

[Laughter.]

DR. LANGER: Yes, exactly. But it seems to me NIH has initiatives where they want to encourage research in the general area of women's health, seems to me--you know, they just established like a new sort of bioengineering and radiology. It just seems to me that that's the kind of research that could get done, you know, and maybe there's models that would be of some value. That's really what I wanted. So then the question is: Could you initiate discussions with NIH to try to--you know, they often put out these requests for proposals to see if people can come up with some good ideas.

DR. WOOD: Yes, they're putting something out. Has it gone out? Not out. Coming out soon. The NICHD is very interested in the concept of sort of pregnancy as sort of--pregnant women as therapeutic orphans, and they--but their interest is clearly much broader than FDA's in

terms of understanding the pharmacology of pregnancy, our interest being, you know, as evidenced by the research that we fund, being fairly targeted at how we're going to get useful information that can ultimately go on a label that can help with dosing and clinical practice, their interest being much broader in terms of the whole physiology, pharmacology of pregnancy and how that interacts with medications. And they are planning to put out an RFA with a very broad mission and a very general RFA in this arena. And I think your point is well taken, that that idea of modeling may not be in there, and it would be something worth to go back and look and encourage them to do because that's an interesting question.

DR. LANGER: Yes, because I would think myself, just speaking for the bioengineering community, and I also think that there's a whole group of people in schools of pharmacy, pharmacokineticists, you know, that that would be a real good challenge, that there might be some contributions that could be made there. So if they were encouraged to do it, you know, that might give you--because it just seemed to me when you were talking earlier, you know, you realize you're talking about changes in fluid and things like that, but maybe there's ways to get some--I don't know--

DR. WOOD: Yes, and depending on where we are, we always need to go a step further.

DR. RIVIERE: There's been studies done on--toxicology studies and teratogens and placental transfer, and I don't remember when, but I've seen PD/PK models of modeling pregnancy, that that kind of work, you know, physiological-based model--

DR. WOOD: And then moving it beyond, because I think the--

DR. RIVIERE: But I don't--that's the problem. Animals and humans is a huge jump.

DR. LANGER: Right, that's one jump. But, see, the other way of thinking about it is--I'm not just thinking about one drug. In other words, I think what you'd like to think about is if you understood certain fundamental parameters, like if you understood the physical/chemical properties of it, like, say, you know, that it will lead to diffusion coefficients, partitioning. You know, so then--and, you know, the half-life then maybe there's some predictions that you might--you know, what I'm thinking about is sort of a simple model--I mean, it wouldn't be that simple, obviously, but could you plug something into the computer some day--

DR. RIVIERE: Some people have done some of that. The problem, again, is it's done in rodents, and then--

DR. LANGER: No, but I'm--yeah.

DR. RIVIERE: --the physiology is so--and you can do that. I agree. But there has been some work done on that.

DR. WOOD: But, again, that's not asking the question about how the physiology of the mother changes in terms of her PK/PD--

DR. LANGER: That's right.

DR. WOOD: It's more placental transfer, which is, again, more akin to the lactation--

DR. LANGER: It's just one question. I'm trying to think about a broader context, I guess.

DR. WOOD: That's an excellent idea.

DR. LANGER: Maybe we can see if there's more answers or suggestions to one, two, or any of the questions. Do people have any other comments on the first or second question, or the third? Do we want--

DR. WOOD: I guess I would also have a question. Does this--you know, we've had the experience both in terms of the labeling regulation and doing this research, that there is a very understandable hesitancy for people to take on this challenge. I guess in terms of how--you know, does explanation relieve that anxiety or is it--you

know, or is it something we're never going to be able to overcome?

DR. FEIGAL: Could I just ask a question on the third one? One informational question. Has there been a prospective registry larger than the acyclovir registry, or is that the largest?

DR. WOOD: That's the largest.

DR. FEIGAL: That one sort of illustrates kind of the problems with the registry strategy because it took them about ten years to get 1,000 exposed women, and then only about a third of those were exposed in the first trimester. And so they ended up with really only the power to exclude a doubling of all birth defects if the hypothesis was that it would cause all those defects to evenly go up, and it only had a power to pick up a ten-fold increase in any specific common birth defect.

And so I think the setting in which exposure cohorts are useful is something to take a close look at, because when we then looked at whether or not that registry should continue to get more power and you realize that power is the function of the squaring the sample size, to double the power we would have had to have gone, you know, to another 4,000 women. Obviously it's a very small fraction of the people who were exposed.

My other question is if you don't start with an exposure cohort, you can start with an outcome cohort, and there are birth defect registries. And if you actually said for a second that, well, most of the exposures identified in the birth defect registry aren't going to be the cause of the birth defects, because we're not making much progress there. But it is an interesting source of information about what drugs those people took, because they very systematically interviewed, and there, when you're interested in the outcome, the dilemma is that they better remember the drugs they took, and so you've got recall bias and you have problems doing causality for the outcome. But if you say I'm not interested in the outcome, I'm interested in finding out what drugs pregnant women are exposed to, and you realize a third of all women--not a third, 3 percent of women have a birth defect, and you've got states where reporting is mandatory, like California, you may be able to get quite a bit of your exposure targets to select the drugs that are feasible to study as a byproduct of some other kind of research. So that's another suggestion.

DR. WOOD: Does OTIS or Mother Risk have that sort of data based on...

DR. MILLER: What pregnant women are taking, the prescription databases do a very good job of telling us

that. So we know what prescriptions are being filled. We don't know that the women are actually taking--

DR. WOOD: But in terms of other drugs as well, the OTC or--

DR. MILLER: And certainly OTIS provides us lists with what questions women have about drugs, what drugs they're concerned about during pregnancy, so we could approach it that way. Usually what happens whenever we try to do a prioritized list is we have one less than every drug that's approved.

DR. FEIGAL: The other comment is that if, in fact, as pregnancy probably is, it's so dynamic that, in fact, it's difficult to lump all pregnancies together to predict PK, it sort of implies that these general strategies of just studying pregnancy as a category may just blur everything together and miss the opportunity to identify certain times in pregnancy where the volume shifts or the metabolic conduction of liver is particularly active and you're not in a steady state, you may misleadingly conclude that everything is just about the same as the general population except the person might be bigger than they look because they've got more volume.

So I think that, you know, your real dilemma is whether to take some of these broad strategies or whether to go back and encourage the NIH and others to study the

physiology in some detail, develop the hypotheses about which of those physiologic states would have the biggest impact on drug metabolism, and then see if you could show that. Then you've got to find something for the clinician to actually figure out when they identify those states and what are the clues that are commonly clinically available. Is it anything as simple as recent weight gain or creatinine or whatever? You know, whatever. But if, in fact, it is such a dynamic state, then the question is how do you get the research for the additional clues so you don't just label everyone for all pregnancy, or as we sort of do sometimes, trimesters. But that's often picked that way because of exposure considerations, not physiology of pregnancy considerations.

DR. WOOD: I think the studies we're doing now are based on trimester. It's not going to go much more in-depth than that.

DR. UHL: Except the population PK study allowed you to work around that.

DR. WOOD: Continuous.

DR. UHL: Right, the time in pregnancy is a continuous variable and you can analyze it that way. That's one of, I think, the reasons why had said that it's probably a better approach.

Additionally, as we're working with these studies, you know, it's very obvious that people need to think what time are they talking about so we don't just lump pregnancy as one time period, because the changes are so significant and so dynamic throughout the whole pregnancy. And Peggy didn't really get into the design issues, but we have addressed trying to really narrow windows if you're going to do a traditional PK approach, to really narrow the windows so you somehow decrease your variability. But, you know, that remains to be seen how--when we finally get the results of that.

In answer to your question about the pregnancy registries, the Swedish Birth Registry has huge numbers of patients and there are publications in the literature from that database where they capture, I believe it's like 97 percent of every pregnancy that occurs in their country. And they have links of the mothers--the mother's file is liked to the baby's file, and they have published several thousand patients with omeprazole, with fudesanide (ph), things of that sort. But as far as American registries, they're not the size.

The registry guidance document is published now in final form, and one of the things that it talks about is when you design your registry, to decide what sample size you will be able to enroll or anticipate enrolling, and also what sample size will give you what power to

rule out, let's say, a two-fold or a ten-fold increase in whatever--either specific birth defect you're interested in or the overall incidence of birth defects, which is the 3 to 5 percent. So to think about the power of a registry at the design phase, not at the end when you've only enrolled 1,000 patients and then say, well, how useful has that been.

DR. MILLER: I think if Diane Kennedy were here, she would insist that we mention we're going to be talking about margins of safety. So we may be just providing women with reassurance, you know, we're sure it's not a two-fold increase in a birth defect. And for me, that would buy a lot, I think. You know, we're sure it's not a thalidomide. We're sure it's not a really bad actor, and you really need this drug. So that's probably what we're going to be able to get for most drugs.

DR. LANGER: Are there any comments from the audience, or questions?

[No response.]

DR. LANGER: Is there any way that would be useful to continue in future meetings any, you know, agenda items you'd want to put on for the future that--you don't need to answer necessarily now, but--

DR. WOOD: There potentially could be; particularly our work with NIH and their RFA might be

something that we could come back to. And then, of course, if we get a proposed labeling rule.

DR. LANGER: Okay. So you might want to consider that for future meetings, but any other things that we should do in this session?

[No response.]

DR. LANGER: Thank you very much. Excellent presentation.

I want to just get a sense from both Janet and the members of the Science Board, would you like to take a five-minute break or just continue? I think people want to continue.

The next topic will be the Pharmaceutical cGMPs Initiative, and Janet Woodcook, who's the Director of CDER, is going to go over that. Janet?

X DR. WOODCOCK: Why don't we get the slides up, Bob? I'll give you some update.

This is a large initiative that FDA announced a couple months ago, and I want to say that this really was an outgrowth of the PAT presentations that we had before the Science Board over the last year. We've had two presentations, and the PAT meeting, Process Analytical Technology, and basically the introduction of new technology into pharmaceutical manufacturing.

That initiative has really taken off. We have had several public meetings on this subject. We have put

together a team between the FDA field organization and CDER that will inspect PAT. We have done training. We have a guidance document that is in development that hopefully should be out soon in draft. And we have a conceptual submission from the first manufacturer, sort of a proof of concept type of submission, and we expect five submissions of actual applications of PAT probably within the next year or so. And we have met with manufacturers about this.

So this is really taking on a life of its own, and what it did really was stimulate us to look more broadly at the pharmaceutical quality regulation in general, using this as kind of an example, the PAT.

So I'd like to go through--I'll try to be quick--what we have announced and what this initiative is about.

So what is it about? And I'll go through the background, some of the themes, some of the things we're going to do, and what we hope to accomplish out of this initiative. And I think you'll be able to relate--those of you who were here at the previous discussions of PAT will be able to relate those two together.

The initiative that we announced is not just about good manufacturing practices, which is the standard for conduct of a quality system in pharmaceutical manufacturing. It's about regulation of product quality,

and this initiative goes across FDA's field organization. And I can see John Taylor is here, the science rep, as well as the Center for Veterinary Medicine, the Center for Biologics, and the Center for Drugs, all of which are involved in regulation of the quality of different pharmaceuticals.

So this is a collaboration, and our system that these units are involved in involves a standard-setting component, a submission review components, an inspectional component. In the standard setting, we set standards for quality of pharmaceuticals, which some of you are familiar with, many of which are in ICH, in the International Conference on Harmonization for pharmaceuticals. They have to do with like stability, impurities and so forth. That's one set of standards.

And, generally speaking, manufacturers have to submit information to the FDA, and those submissions are reviewed against the standards to make sure that they meet standards.

Then we have the standards for quality systems approach to manufacturing, and that is the cGMPs, or current good manufacturing practices standards. And the field organization and to some extent some of the folks within the Centers go out and inspect the facilities against these standards, against the GMP standards. And that's the system, and this system is supposed to work

together--the whole point of it is supposed to be to make sure that the quality of drugs, animal drugs and human drugs, in the United States is high and those drugs are all fit for use.

Now, what this initiative is doing, we're stepping back and we're looking at this, and we're asking how effective is this system in achieving its objectives today. Are we achieving its objectives and are we achieving them efficiently? And we have to step a little bit further back and ask what are the objectives in terms of specifics. What does quality mean in terms of a pharmaceutical? And how do the component parts of the system operate and cooperate, and do they cooperate, and how effectively? So that's what this is about, to step back and look at both the submission part and the inspection part of the quality system and see how it's functioning.

Now, why are we doing this? This system was devised many decades ago. The last rewrite of the good manufacturing practice regulations that was significant for pharmaceuticals was about 25 years ago. So a lot has happened since then. And I would say the submission review part and the ICH part has kind of grown up over the years, the way we do that.

There have been incremental adjustments over the 25 years. We had the major revision in 1978 of GMPs.

The Center for Drugs and the field had an agreement on kind of who would do what in the 1990s, and that was more like a peace treaty. And we had a SUPAC, which is scale-up and post-approval changes. That was a series of guidances the Center for Drugs issued in the '90s, and those had to do with what types of changes you could make in your manufacturing without doing a submission and which ones required a submission. And the FDA Modernization Act in '97 brought some changes, required changes as well to our regulation, and then there's a concept of team biologics, which involved the biologics staff had done their own inspections and the field--in the drug area, and the field personnel worked with the biologics folks, and that was a team biologics concept.

So all these changes had occurred, but we hadn't really stepped back and looked at the entire system. But the environment, while the system has sort of incrementally changed and grown, the environment has really changed significantly. Not only are there a lot more approved medicines, hundreds and hundreds, of course, more approved medicines than before, but their role in health care has become central over these last few decades rather than an adjunct to hospitalization and surgery.

There have been--and we've discussed this in PAT. There have been a lot of advances in both

pharmaceutical sciences and our understanding of these substances and their properties, as well as manufacturing technologies, and particularly in other sectors. There have been advances in the science and management of quality. The GMPs are a quality system, but, in fact, there's been a quality revolution in the past 30 years in other manufacturing sectors, and so there's a new understanding of how you bring about quality compared to the understanding in the '70s and how does that apply to our understanding of the GMPs.

Biotechnology is being used much more broadly in a very wide range of applications, and the industry--back in the '70s, we were regulating a domestic industry, primarily, and that's how it was conceived. That's how the inspectional--that's how the programs were set up. This is totally out the window now. We're regulating a global industry, and that really changes or needs to change the approach for a variety of reasons. It stretches us very thin in our inspectional role.

For example, this is domestic inspections. I don't know whether you can see this. These are the non-medical gas type of inspections, inspections of regular pharmaceutical manufacturing, not pre-approval inspections but regular post-approval, good manufacturing practice inspections from 1980 through current. And you

don't need to look at all the numbers. You can see the trend. The trend is down.

We cannot stretch our resources across the number of plants and so forth. The inspections are more complex, and actually we probably have fewer resources to bring against this. So the bottom line is we can be in plants less often and in fewer plants than we were in 1980, and this trend has continued over the decades, in more or less an unremitting fashion, although it may have flattened out a little bit recently.

And so this is another environmental change that we must recognize as we go about looking at our system. We can't be there. But, in fact, with all the changes in technology and scientific understanding, maybe being there isn't--maybe we can devise a system where being there isn't quite as important as some other thing as it used to be.

Now, in devising this initiative, we have some major themes and principles. First of all--and this is something that there's--more understanding has grown up, I think, over the last 20 years about a risk-based orientation, and this means a number of things. We really need to make sure we put our resources--not all of our resources, but we put the bulk of our resources against the riskiest areas, and that would seem intuitive. But, in fact, back in the '80s when we could

sort of cover everything uniformly, that was not the approach. So we really need to make sure that the amount of resource put against any given area is proportionate to the risk to the public, the public health.

But the same thing goes to the requirements that we have, and this is the public standards. It used to be that our requirements might be limited, say, by analytical methodology, and the limit of an analytical test might be something, 1 percent or something, one part per million or whatever. Well, it may be with excruciatingly sensitive instrumentation we have nowadays you could detect many, many, many orders of magnitude less. But that doesn't necessarily mean that that should be the limit, and when you're not limited so much by your analytical techniques, then you have to think about risk, and that needs to be your criterion.

In general, the more scientific understanding we have about manufacturing and what the critical variables, critical control points, whatever, within manufacturing, the more we can tailor our requirements to the vulnerabilities and make sure the vulnerable sectors are controlled and not simply have blanket requirements about everything, because we don't know where the risk is. So that's one big piece.

Another piece is that to the extent we can, we base our regulatory requirements on the best available

science. And, again, in the 30 years that have elapsed or the 25 years, we have gained quite a bit more scientific understanding in a lot of the areas that we're talking about here, formulations, a lot of things. And we need to not only recognize but, in general, we think we need to facilitate introduction of scientific and technological advances, and those of you on the Science Board who listened to all the discussions on process analytical technology, I won't belabor this point because that's the exemplar of this. But I want to say it's not limited to PAT. PAT is simply the example of why we should facilitate introduction of this science and technology because it does have the opportunity to achieve better quality at no increased cost or maybe cheaper.

Another theme, of course, is that in doing this initiative we plan to maintain our traditional stance of strong public health protection. We don't think doing this initiative will interfere with current enforcement activities in the manufacturing realm, and we think achieving our objectives under this initiative will actually result in better public health protection.

Another principle, we have talked to our international colleagues in other regulatory authorities and we've talked to the folks in ICH, and we plan to

cooperate internationally because this is now a global industry that we're talking about.

Now, another principle that we plan to follow as we look at this is the integrated quality systems orientation to our approach, and that sounds a little jargon-y. What do I mean by that? Well, first of all, as I already said, we're going to look at innovations in quality systems outside the drug sector. And we'll be doing some benchmarking in some very different sectors and areas where at least people claim that certain quality systems approaches have given them quantum improvements in quality. And we're going to bring those folks in and talk to them and see about the application of quality systems from the quality revolution. And I personally can testify, in cars, I'm old enough to remember when you bought a car and, you know, first the handles fell off, and then it stopped on the highway, and then all these different things happened. Yes, and then some people came along from other countries and they made better cars that didn't break all the time, and they claimed that was from their quality systems, that they made a good product every time or most of the time. So we want to look at that thinking and what kind of thinking is that and is that inherent in our approach to quality systems.

Second of all, though--and this is, you know, courageous of us, I think--we're going to look at our system of regulating drug quality. Is our system a quality system? Does it have the attributes? Are we delivering a good quality product as we do during regulation in the quality area? And is it an integrated system? In other words, do we work with the field, do we work with the other centers?

One of the issues that has been raised by various parties is of inconsistencies. A good quality system will surface and address inconsistencies. So we're going to see, and we're starting this effort. It's very interesting.

Now, we're going to have some immediate steps as we do this. We plan to hold a series of scientific workshops with key stakeholders. That's on the science area. We've already had a first Advisory Committee meeting of Pharmaceutical Sciences, but we had all the different centers involved in everything on aseptic processing. This is one of the areas, making sterile drug products and what are the parameters and how do you do environmental monitoring and what do we know about all these things. And we will be hopefully issuing guidance on that and having more scientific input on that.

We plan to hold a major workshop in the spring, and that will have many different--it will be partitioned

into many different areas, and have discussions on different science issues, and we will invite academia and industry to come in and tell us what scientific areas we think we should focus on, what are the issues. So we will be holding a lot of scientific discussion and input over the next year or so.

We plan to enhance scientific and technical expertise, and we have been doing that. In the Center for Drugs, we have hired--we feel we need our chemical engineering and we need more engineering input, and some other kind of specific technical expertise, and we are working on acquiring that expertise. And we'll probably be involved in training people who are here and bringing up their level of understanding of some of these things.

Encourage greater use of comparability protocols. Comparability protocol is a way a manufacturer can, if they modify their product somewhat or their process somewhat, they can demonstrate maintenance of quality and not have to submit something for FDA to review, because FDA has vetted this protocol.

Increased use of product specialists and inspections. As I said, the product specialists, the scientists in the Biologics Center, often go out and are involved in inspections. We have always wanted, I think, in the other Centers to have the scientific reviewers also participate inspections. So we'll be doing more of

that. And these are things we plan to--all plan to initiate these within six months of the announcement, which was in August.

We are centralizing the technical review of warning letters. Warning letters are letters we send to firms that have specific technical cites of violations, and this is a way of trying to understand do we have inconsistencies or not because of the issue of inconsistency. If we see areas in these warning letters where we have disagreement, then these are things that we need to bring some scientific expertise to bear on, perhaps issue guidance on.

The next one is probably not of great interest to this group. The Part 11, the third bullet here is the regulation on electronic records and signatures. This is also somewhat a science issue in the science of validation and computer science, and we are--the field has been the lead on this for a while. CDER is going to take the lead, kind of take up the baton for a while, and we're all working very hard on this to try to get this settled because we feel this is another area where the incorporation of new technology may be inhibited because of uncertainty about where FDA is going on Part 11. So we have made this a very high priority for us to get some guidance out there, to get some resolution of some of the issues around Part 11.

This directly relates to process analytical technology because acquisition of data online or at-line sensors, you know, this is a computerized, an automated function, and we need to have guidance on how much data need to be archived and the technical requirements around that data.

And develop a technical dispute resolution process. This means when there's a citation by the field inspector or the other people who go out in the field, an inspector in the firm feels there is a scientific--has a scientific disagreement with that conclusion, there would be an appeals process so that we could get a board or whatever involved in this appeal, and we could discuss the underlying principles. And, again, this may help us in many ways. It helped me, helped us signal which scientific areas require some attention and perhaps issuing guidance.

Again, you know, work planning process, we're currently altering that, and that's not as much interest to the Science Board, but we will be trying to use at least our crude approximation of risk, and we're trying to develop better data, surveillance and other data, so we can develop better models of risk, so then we can--the work plan actually tells the inspectors what to inspect this year, where should they go, what should they look

at. And we need much better data acquisition and data analysis to help us target according to risk.

Then the Biologics Center is doing with the field an evaluation of the team biologics concept and how that has played out.

Now, the approaches we're taking--I don't want to take too much of your time, but we're going to do a contract that will be external to us and both to evaluate our process and perhaps assist us in evaluating some of the science aspects of our regulation. And we also hope to collaborate with academic groups because we can't directly evaluate industry. But in other industries, there are academic groups that actually study the industry environment and the business conditions and so forth and the relation to quality systems and so forth, and we would like to collaborate and encourage the development of that type of evaluation. And, of course, we would collaborate with the industrial sector in getting this done. But we wouldn't carry out that type of study ourselves. I don't think anybody would be willing to talk to us.

Also, you know, we are going to do benchmarking, as I said, within the contracts. We're going to look at quality systems. We're going to benchmark other areas, other sectors as far as how they do standard setting. And we also want to benchmark audit and surveillance

functions, of which there are a number of other government agencies, as well as other large purchasers and so forth that need to maintain quality amongst their supply chains or, you know, other--we're going to cast a broad net and look at these things.

The science review, we're going to look at all these types of science, not just the science behind the product itself, but the science of quality, what is known there, and the science of risk management, which the Drug Center has already spent a lot of time on risk management in the realm of the safety of medicines. So we have a lot of that expertise that we've acquired that we can transfer to this.

We're also going to work with the field and think about can we have a more dedicated crew to some degree of pharmaceutical inspectors. The field now--John, you have 4,000 people in the field? Yes, there are 4,000 people, and that's very daunting to us to think--you know, to train so many people, or get to know them and have a one-to-one relationship with them. So it's really trying to identify a group of people who really consider themselves pharmaceutical inspectors and that we can co-train with and center in the field, and I know the Veterinary Center is also quite interested in this.

As we go along with this, one of the real focuses, as you probably gathered, is to issue guidance

in this area. There's a lot of guidance, as I said, in the product quality area under ICH, such as stability and impurities and things like that. But there isn't as much guidance in the quality system area and the GMP area, and we think we need to get a lot more things written down and laid out. So we'll be doing that, and our compliance programs, which are actually the directions to the field inspectors about what they go out and inspect, will be revised, and we expect to do a lot of education and training with industry and the FDA as well as across the FDA Centers and groups that are collaborating, and then we probably will be issuing new policies and procedures. And we might have to work on regulations. That's up in the air. We have a lot of scope within the existing regulations, but we may at the end of the day find that we need to revise regulations, and if so, we will assess whether we should do that.

We're setting up an Evaluation Group to evaluate this effort, and first of all, we have to identify what the problems are and what we expect to accomplish, and then we'll evaluate ourselves against whether we accomplish it.

Broadly, we would like to demonstrate a move to risk-based approaches in our operations, that we have an overt culture of assessing risk and devising our programs based on as objective risk as possible. We want to

demonstrate that we have actually enhanced the science base under which we operate in this area. We'd want to demonstrate better integration between submission review and inspection programs. We'd like to show that these are tightly linked and operate as a system. And we'd like to be able to demonstrate that the industrial sector has actually gone ahead and adopted new technologies, and we are at least seeing the beginnings of that within PAT that that's actually happening.

Immediate steps that I listed, we hope to accomplish by February 3rd. That doesn't mean we're going to solve Part 11 by February 3rd. It means we're going to transfer--accomplish a transfer to the Center for Drugs for the lead and probably have some of the initial work done on Part 11 and so forth. So those steps that are laid out, those initial steps will be accomplished, we hope.

We would run this project for two years' duration from August when it was announced, and August two years from now we're going to stop and we're going to evaluate it, and we're going to have the report of the Evaluation Group. And we can report back to the Science Board if the Science Board is interested. But at that point, we'll see whether it's worth continuing, what have we accomplished and do we have more to accomplish.

The Evaluation Group has been convened and is asking a lot of hard questions. We have many working groups that are working, and we're going to be seeking a lot of input from industry, which we've gotten some already, and academia along the way as we move along in this.

So that is a general outline of what we're going to do. We aren't ready really for specifics yet. We're getting into that right now. But I think we all feel good this was kicked off by the discussions of process analytical technology that we had over the last year before the Science Board.

Thanks, and I'm ready for questions.

DR. LANGER: Thanks, Janet.

Questions or comments? Harold.

DR. DAVIS: Having been on the Board at that time, you've come a long ways, pretty good.

Two questions. You've mentioned that industry has been involved and commented. What's been the nature of the comments so far, positive, negative, wait and see, whatever?

And my second question, I'm very much interested in your Part 11, and I'm not sure I appreciated what you thought the mood would do. I heard you say it, but I'm not sure it was clear to me. Would you restate what you're trying to accomplish there for me?

DR. WOODCOCK: Right. Well, in the first part what does industry--well, basically we've heard from various groups. We're received some documents from people with suggestions on what we should work on. That's what we've heard from industry, along with what has been discussed in the open public meetings we've had both on PAT and aseptic processing. We will open a docket on this, a public docket, so that we can put all the comments within the docket, and people can see what everybody has said about it and what people's issues are. But mainly right now, from industry, we've received suggestions on what the highest priorities might be, Part 11 being one of them.

On Part 11, I think what we all bring to this--and John is here from ORA--and all of us, is that we have a will to get this resolved. And CDER, because of the PAT initiative and because of our electronic submission, our paperless review process, we recognize we must resolve the Part 11 issues and move on. And so we are committed to getting closure, to getting to a point where we understand the requirements, and we can promulgate them, and everybody can be on the same page about what the Part 11 requirements are and how to comply. That's really what we need.

John, do you have any comments?

MR. TAYLOR: No. I think Janet articulated quite well the rules that existed since 1997. In light of the fact that the Agency at one time was issuing its guidance verbally, there was recognized a need to formalize the guidance process, and more importantly, a need to resolve the outstanding issues that have prevented companies from adopting this type of approach, because both for reasons of economics, efficiency, for product quality and for other reasons, it's important to integrate these e-commerce principles, and we feel a need to resolve those issues so that we can not only facilitate those goals externally, but also internally in regards to our use of electronic submissions.

DR. DAVIS: Does that mean by any chance that because of your recognition or concern, that there is this cloudedness about it so far, that until you come out with some clarity, that CFR Part 11 inspections or 483s won't be issued, there's some hiatus until that time or what?

MR. TAYLOR: Yes. There has been what's called a Compliance Policy Guide in place since 1999, where the Agency has basically stated that we're exercising enforcement discretion until these outstanding issues have been resolved. So to the extent that 483s have been issued with Part 11 issues on them, those are just educational. They're not for the purposes of furthering

an enforcement action. In a few rare cases there have been warning letters where the underlying problems were so pervasive that no matter what interpretation you took regarding Part 11, that basically these are situations where there was almost no system in place at all, but for the most part, the only thing that we do is we issue 483 items for the purposes of education. We're exercising an enforcement discretion, and the reason for that was because the Agency recognized that there were outstanding issues that needed to be addressed. And in all fairness, it was unfair to hold people to a standard that we couldn't articulate ourselves, and that's what we're trying to resolve.

DR. DOYLE: Very well done, Janet. I'm curious to know a little bit more about the risk assessments that you're doing. Is the purpose of these risk assessments to identify what products are of greatest risk or what points in the process are riskiest, or where are you going with that?

DR. WOODCOCK: There are three kind of meanings to this, okay? And, yes, the first would be for our inspectional program, where are the greatest vulnerabilities to public health? Because as you saw, we're not the Department of Agriculture and we don't have an inspector in every plant. And the number of inspectors and the number of inspections that have been

able to be done over the years have dwindled. So we need to figure out what are the most serious vulnerabilities with respect to public health, and make sure the resources are concentrated there. I want to make sure people understand that doesn't mean they would be exclusively focused on the highest risk. We would continue to have a presence throughout any risk categories, but the emphasis ought to be on the highest risk products.

Now, that doesn't mean we could say today, well, intravenous products for life-threatening diseases are highest risk. We think we probably need to construct a model that has to do with the firm's compliance history--I'm just making stuff up because I don't know the answer--the inherent difficulty in manufacturing the product. You know, sterile products obviously are of more concern than toothpaste or dandruff shampoo. There are other factors that go into this, but we need to construct such models and then test them and so forth. So that's what we're talking about for inspections.

For manufacturing, it's quite different, although it's conceptually the same issue. And Ajaz taught me a lot about this. So back when much of this was conceived, perhaps back in the '70s, we didn't have as much basically engineering and material science understanding, especially for solid oral dosage forms,

about what the factor were that create vulnerabilities that make things go wrong. For example, a blender. Why is there an inhomogeneous blend? And we didn't have the ways of monitoring blend that we may be able to introduce today. So the approach was we need to check everything and control everything carefully and control the process extremely carefully, because we couldn't predict which factors mattered.

Now, as more knowledge has been generated, scientific knowledge, and you can predict, based on all sorts of things that I won't go into, certain failures because of certain parameters, those are the parameters that should be controlled the tightest and we may be able really to move to a system that really focuses on the risk or critical control points of vulnerability in the manufacture of many products. This would help everybody. It would help FDA because we wouldn't have so many records to inspect. There's a record burden for everyone here in all this testing and controlling and record keeping and everything, and it would help the manufacture because it would be more efficient, and it would help the consumer because you would have at least a high of assurance of fitness for use, maybe higher. So that's another meaning of risk. And we are exploring all of those parameters and thinking how do you apply this in a regulatory system.

DR. LANGER: Other questions or comments?

[No response.]

DR. LANGER: I just had a minor one. First, again, it's great progress. You had mentioned about--and this is really just to see if we can help in any way--getting chemical engineers involved and stuff like that. Is that going fine or is there any help you would like?

DR. WOODCOCK: This is H.S. Hussain from the Center for drugs.

MR. HUSSAIN: This is Friday, casual day, so.

[Laughter.]

MR. HUSSAIN: I think we have been able to recruit chemical engineers and enlisted pharmacists, and we actually have set up a position description for that, and we will have some challenges with respect to people trained in pharmaceutical engineering, and support for education I think is needed, so I think the Science Board has a voice in that regard with respect to making arrangements of this with NSF and so forth.

DR. WOODCOCK: Yes. We can come back to the Science Board at some point as we get to specific science issues. I think what H.S. was right now we're able to recruit, but there may be like more fundamental science issues that we really need to bring back to the Board and get some help, perhaps research support for certain kinds of research that really needs to be done.

DR. LANGER: That sounds great.

Any other questions from anybody in the audience or Board?

[No response.]

DR. LANGER: Janet, I think everybody thinks that's great progress. Thank you.

DR. WOODCOCK: Thank you.

DR. LANGER: So now, basically, this is the final session where we just make closing remarks and talk about future directions, so let me try to make some summary comments on each section. If I'm missing something or state something in any way someone would like me to change, correct me.

So the first topic was counterterrorism. The issues that came up there were to explore the issue of research priorities and counterterrorism and how the Agency's priorities--prioritizes those with limited resources, also to explore how the Board can help, for example, with respect to capturing expertise from academia, for example. Any changes on that?

[No response.]

DR. LANGER: The second area was in the Office of Cellular, Tissue and Gene Therapies. Let me go over what we talked about there. There was a lot of discussion with the following comments came up. First, that the Board believes that as part of its function,

that if administrative changes are being considered which could potentially impact the science basis of the FDA, the Science Board should be asked for input, and that specifically on the proposed move of the therapeutic products from CBER to CDER, the Board's concerned that the science not get disrupted and wants to better understand the reason for the move.

Any comments, changes on that?

[No response.]

DR. LANGER: The next point was there was a--and that also came up in the open public comment.

The next topic was on pregnancy and labeling issues, here that the FDA will explore opportunities for further research with NIH and will consider how the Board can help and continue to discuss this issue at future meetings.

Any changes, modifications?

[No response.]

DR. LANGER: The next section was pharmaceutical cGMPs Initiatives that Janet just went over, and I think here everybody is really delighted with the progress and look forward to any way we can help at future meetings.

And finally, came up, just for the future, other proposed items that might be discussed at future meetings would include combination products. These are not to be meant exclusive in any means, but combination products,

counterterrorism follow-up issues as aforementioned, antibiotic developments from the April meeting earlier this year, obesity issues, further exploration of the pregnancy labeling issues.

And Mike Doyle, as the new Chair in 2003 will work with Susan and Norris to prepare agenda items in consultation with other members of the Board.

Any other comments or addition to that?

DR. DOYLE: Did we want to include the topic about the Committee regarding reorganization at that meeting?

DR. LANGER: Yes. What would be the best thing to say about that? I guess that was kind of left--I don't think that was clear from what was said this morning, what was going to happen, but maybe that could be part of what's going to be--when you work with Susan and Norris on that agenda, that could certainly be a part of it. Whether we need to say it more explicitly, I don't know. What do you think?

DR. DOYLE: I just didn't want to lose the thought.

DR. LANGER: Do you want us to do that?

DR. ALDERSON: I would counsel you to go ahead and say that--what I hear from the Board members this is something we would really like to engage in if this is

something the Agency wants to do, and offer your services for that.

DR. LANGER: So I'll put another item there. Basically discuss--what should I say? What would be the best way to say it?

DR. DOYLE: Restructuring of FDA.

DR. LANGER: Discuss restructuring of FDA from a science standpoint.

DR. DOYLE: Exactly.

DR. LANGER: From a science based standpoint. We'll put that down as a future item as well. Any others? Yes, Harold.

DR. DAVIS: I would like for Janet to consider--I really applaud the CFR part 11. I'm not sure the whole Board appreciates what that's all about. For those of us in the industry I mean it's just critical. And so I would like to consider in the future, especially as you get past February the 11th and about to make some comments, decisions or whatever, so I'd like to have you share those with us just because I do recognize how critical those are. And I'm very happy you're doing it, that's for sure.

DR. WOODCOCK: Yes. I would be glad to do that if the Board is interested. We are crashing on that part of the project because it is so critical, but we don't

have anything to share right now. It's going to be a little while.

DR. DAVIS: whenever.

DR. WOODCOCK: When we have something, we can share it. Again, it's very technical, not that you guys can't understand it.

[Laughter.]

DR. LANGER: You have to tone it down for us.

[Laughter.]

DR. LANGER: So what I wrote, I basically just amended what I had said earlier. I just wrote, "Excellent progress on the pharmaceutical cGMPs, and we look forward to following this more appropriate at future meetings." I didn't add the fact that we want it to be very simple. Is that all right?

Anything else that anyone would like to add before we adjourn? Yes?

DR. SCHWETZ: I would for sure want to thank you, Bob, for not only a good meeting today but many of them, and the help that you have been to us, and we look forward to a similar performance by Mike.

DR. LANGER: Well, it's really the work of you all and the FDA, so it's been a pleasure.

DR. DOYLE: I want to second what Bern said, and the representative Board has really appreciated your leadership, Bob.

DR. LANGER: Well, thanks. It's been a pleasure to work with all of you.

[Applause.]

DR. LANGER: With that, any other topics?

[No response.].

DR. LANGER: I guess we'll move to adjourn. We'll adjourn. Thank you all.

[Whereupon, at 3:18 p.m., the meeting was adjourned.]