DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

FDA SCIENCE BOARD ADVISORY

COMMITTEE MEETING

Thursday, November 6, 2003

8:00 a.m.

Room 1066

5630 Fishers Lane

Rockville, Maryland

PARTICIPANTS

Michael P. Doyle, Ph.D., Chair
Jan Johannessen, Ph.D. Executive Secretary

MEMBERS

Robert M. Nerem, Ph.D.
Martin Rosenberg, Ph.D.
Jose C. Principe, Ph.D.
Cecil B. Pickett, Ph.D.
Jim E. Riviere, D.V.M., Ph.D.
Cato T. Laurencin, M.D., Ph.D.
Katherine M.J. Swanson, Ph.D.
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Mark B. McClellan, M.D., Ph.D.
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Robert L. Buchanan, Ph.D.
Daniel Casciano, Ph.D.
Kathryn Carbone, M.D.
Linda D. Youngman, M.S., Ph.D.
Subhas G. Malghan, Ph.D.
Anne M. Kirchner, J.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. DOYLE: Good morning and welcome to our Fall meeting of the Science Board. It looks to be a full but exciting agenda. We are going to hear about food security and what the agency is doing in addressing food-security issues.

But, before we get into that, I think we should first introduce ourselves and who is at the table. I am Mike Doyle. I am Chair of the Science Board and I am a food microbiologist at the University of Georgia.

Dr. Laurencin?

DR. LAURENCIN: I am Dr. Cato Laurencin from the University of Virginia, orthopedic surgery, chemical engineering and biomedical engineering.

DR. THOMAS: John Thomas, Vice President, Retired, Professor Emeritus, University of Texas, San Antonio, pharmacology, toxicology.

DR. SWANSON: I am Katie Swanson with General Mills. I am a food microbiologist.

DR. PRINCIPE: I am Jose Principe. I am Professor of Electrical and Biomedical Engineering at the University of Florida.

DR. PICKETT: I am Cecil Pickett. I am President of Research and Development for the Schering-Plough Corporation, also a biochemist.

DR. RIVIERE: Jim Riviere. I am a Professor of Pharmacology and Toxicology at North Carolina State.

DR. NEREM: I am Bob Nerem from Georgia Tech. I am a bioengineer.

DR. ROSENBERG: I am Marty Rosenberg. I am also retired from GlaxoSmithKline, infectious-disease bacteriologist and teach at the University of Wisconsin.

DR. JOHANNESSEN: Jan Johannessen. I am the Executive Secretary of the FDA Science Board.

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

MS. GLAVIN: I am Margaret Glavin. I am the new Assistant Commissioner for Counterterrorism Policy at FDA.

DR. BUCHANAN: Good morning. Bob Buchanan, CFSAN, Senior Science Advisor.

DR. CASCIANO: Dan Casciano, Director for National Center for Toxicological Research.

DR. CARBONE: Kathy Carbone, Associate Director for Research, Acting, at CBER.

DR. YOUNGMAN: Linda Youngman. I am the Director of the Office of Research in the Center for Veterinary Medicine.

DR. MALGHAN: I am Subhas Mulghan, representing Dr. Feigal who is on travel. I am from the Center for Devices and Radiological Health.

MS. KIRCHNER: I am Anne Kirchner. I am Regulatory Counsel in the Office of the Associate Commissioner for Regulatory Affairs.

DR. DOYLE: Thank you, one and all, for being here today. Just a few housekeeping things before we get into the meat of the matter. In order to talk, push the button. When you are done talking, push it off. There is too much clutter in the background.

Next, Jan has some waiver information he would like to share with us.

Conflict of Interest Statement

DR. JOHANNESSEN: Good morning. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made part of the public record to preclude even the appearance of such at the meeting. The Food and Drug Administration has prepared general-matter waivers for Drs. Doyle, Nerem, Rosenberg, Riviere, Laurencin, Swanson, Principe, Pickett and Thomas. A copy of the waiver statements may be obtained by submitting a written request to our Freedom of Information Office. The waivers permit them to participate in the meeting's discussion of the FDA's Food Security Program and food security research efforts.

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

The participating committee members have been screened for their financial interests as they may apply to these general topics at hand. Because general topics impact so many institutions, it is not prudent to recite all the potential conflicts of interest as they apply to each participant. The FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

We have open public comment scheduled for 1 o'clock. I would just remind everyone to turn your microphones on when you speak so that the transcriber can pick everything up.

DR. DOYLE: Very good.

Next, we are going to hear from the Commissioner of FDA, Dr. Mark McClellan.

The podium is yours.

Welcome and Opening Remarks

DR. McCLELLAN: Good morning. I would like to thank Dr. Doyle not only for introducing me just a second ago but for his service to this

advisory committee. Over the past four years, Mike, you have done an outstanding job counseling FDA on complex scientific issues, on emerging trends, on helping how we can best shape our responses to the new and challenging public-health threats facing this country, and new opportunities for improving public health. So we very much appreciate your service, most recently as Chairman of this committee.

I would also like to thank the other departing members of the Science Board. We have a set of plaques to present you with. We begin with Dr. Doyle, if you don't mind coming up here. We don't give out a whole lot of good FDA souvenirs but this is one of them.

This, like the other plaques that we will be giving out, is a memento for the work that these advisory board members have done. Dr. Doyle, research recognizes you for your distinguished service as Chairman of the Science Board for the Office of the Commissioner at FDA.

Mike, thank you very much for your

service.

DR. DOYLE: Thank you very much. I appreciate it.

DR. McCLELLAN: If Bob Nerem could come up, please. Bob has been serving with us for some time as well and has long been an advisor to FDA and our scientists. Bob, thank you very much for your service. It has been a pleasure working with you.

DR. NEREM: My pleasure.

DR. McCLELLAN: Dr. Martin Rosenberg, as well, has given years of service to this committee and years more and work on scientific issues related to FDA's major concerns. Martin, we really appreciate your service as well. Thank you so much.

DR. NEREM: I was just getting started.

DR. McCLELLAN: Dr. Harold Davis is also rotating off the committee. He has been a valuable contributor to FDA's efforts as well.

This is also a good time to recognize Dr. Doyle and Jim Riviere for their introductions into

the Institute of Medicine. Just a couple of weeks ago, it was announced that not only they were elected but my Deputy Commissioner, Dr. Lester Crawford. And I also made it in somehow. So this was very, very good year for FDA at the Institute of Medicine. I think that is just a sign of how important the work that we are doing here and the work that our scientific advisors are doing to improve the public health of the nation. Four people closely connected with the agency has got to be some kind of record for a federal agency in one year and I think it is a real testament to the work that you all and Les are doing to help improve the health of this country.

At this point, I would also like to introduce a new staff member at the FDA who is working very closely with me. She is not a new face when it comes to food safety in this country, but her contributions now on our overall counter-terrorism strategy at the FDA are bringing her career to a new level of achievement in helping to improve the public health.

Maggie Glavin is our newly appointed Assistant Commissioner for Counter-Terrorism. She is, as many of you know, a nationally recognized food-safety expert. She was with USDA for more than thirty years, I think, altogether--you certainly don't look it--where she held a number of key positions there, Acting Administrator of the Food Safety and Inspection Service included among them. That is a 10,000-person regulatory agency responsible for public health when it comes to the safety of the U.S. meat and poultry supply. So we are delighted to have Maggie here.

I remember when I was talking with her earlier this year, she had just moved out of government service, thought she would have a little bit of relaxing time in a think-tank for a couple of years. But we managed to drag her back in. I am very glad we did. This is a critical time for food security and for developing better medical treatments for the agents of terrorism and we really need the leadership from someone like Maggie right now.

As I said, it is very good to have her aboard. In the aftermath of September 11th, as we are more aware than ever of the serious challenges to our public safety and national security today, not just from what can go wrong in terms of illnesses and other threats to public health but what people might deliberately do to harm Americans. This is something that we need to think hard about every day.

Maggie, with her experience in safety issues is an ideal person for thinking about how we can continue our traditional mission of protecting food safety while expanding it to encompass major food security concerns as well. It is that kind of comprehensive scientific thinking that I hope will continue to be a hallmark of FDA's efforts to address new challenges like the challenge of counter-terrorism.

This is important because these terrorist challenges not only harm public health and safety, they can also have serious adverse consequences for the American economy and the global economy.

Someone with Maggie's experience can help us think about all that very effectively.

As I said, our mission today, when it comes to food safety, is also about food security. In response to the threats of terrorism, we are implementing new steps in food security that amount to the most fundamental enhancements of our food safety activities in more than thirty years. You all spent some time hearing about the steps that we are taking, particularly in our research programs yesterday.

There are some truly new and important areas of research development where we have not focused in the past and no one else has either but that are very important for addressing when it comes to finding ways to make our foods not only safer but more secure.

We are also taking steps, not only in developing better science and better knowledge to protect the food supply but also in implementing new programs to protect our food safety and security.

We announced two regulations, final regulations, just a month ago that are critical as part of this effort. They reflect our efforts to come up with 21st Century solutions to 21st Century security problems. In the first regulation, we are going to be taking new steps to implement prior notice for foods coming into this country so that we will know ahead of time about all the shipments coming in. This is a reflection of legislation passed by Congress last year that gave us new authorities to obtain and analyze this information as well as new resources to help protect the security of our food supply.

In implementing this regulation, we had to balance and consider two different kinds of concerns. One is the need for having a comprehensive system for being aware of the foods coming into this country ahead of time so that we can target our limited resources more effectively to identify and prevent safety threats from potentially risky foods coming into the country.

The other is to make sure that we do not

have any unnecessary adverse impacts on the large and growing food trade coming into the United States. More than 20 percent of all imports into this country are foods of one kind or another that would be affected by this regulation and the growing diversity and richness of our food supply is creating many opportunities for Americans to live better lives, get more diverse products at lower costs and higher quality. So trade is extremely important to us.

So, in implementing the regulation, we took new steps. We formed new partnerships with the U.S. Bureau of Customs and Border Protection to make sure that we are integrating our resources efficiently at the border. We took new steps to adopt modern information systems for managing the information on products coming in to this country.

As a result of these steps, we are going to be able to implement these regulations with only a minimum amount of disruption in products coming into this country. For example, we only need notice of foods being trucked in, which is a large

part of the food supply coming into this country, only two hours ahead of time and we can completely do our job of screening these shipments for their potential threat, taking a closer look by our experts at FDA because they are going to be integrated into this national information system along with the Bureau of Customs and Border Protection, and then taking action, if appropriate.

The second regulation involves giving us the ability to know who all is involved in the food distribution system in the United States. For the first time ever, we are requiring registration of everyone involved from between production on the farms and when foods get to their final users or restaurants or grocery stores and the like, everybody between those two points, so if there is a foodborne outbreak, we will know who to notify and how to get hold of them quickly if it affects a product that they have been involved with. So this gives us a much better ability to contain a foodborne outbreak if it occurs and also to contact people in the private sector who are involved with

the production and distribution of food that may need to know about potential threats or safety concerns.

This registration rule is also being implemented using 21st Century technologies. It just takes a matter of minutes to register with us over the Internet. That can be done 24-7 from anywhere in the world.

We are conducting the implementation of these regulations with a major outreach effort as well, internationally, so that everyone knows what is expected of them. We are going phase-in the full enforcement of these regulations over time to make sure that everyone has a chance in a reasonable time period to come into full compliance.

Altogether, these regulations will enable us to provide much better protection for the security of America's food supply but they will also help us respond much more effectively and prevent much more effectively naturally occurring foodborne-illness outbreaks as well.

So these are a true milestone for our food-security efforts and, along with the food-security research programs that you heard about yesterday, we were working hard to get a comprehensive food-security plan in place, a plan that addresses everything from vulnerability and threat assessments to detection and outbreak prevention to emergency preparedness and response. You are going to hear much more about that strategy this morning.

It reflects a science-based life-cycle approach that we are trying to take at FDA to assure the safety of food products. This is all based on a core FDA principle of efficient risk management. The idea is to use our limited resources to provide the greatest protection for the public health with the least additional cost for Americans and for our trading partners.

So, with a strong plan and strong leadership and strong support from our partners and industry and governments and our partners from around the world, we are well on our way to giving

Americans much better protection against the treats of terrorism through their food supply.

I would also like to thank the Science Board for your support in helping the FDA to carry out these important activities. As you know, the Science Board has a critical role, an increasingly important role, at the FDA. We need your help to make sure that we are infusing the right, the best and the latest science and necessary technical insights into FDA's programs across the board and that nowhere is that more important than in our Food Security Program where we need to rely on the best and latest science to make it a success as you have seen in the regulations that I have just described.

We have been very grateful for the Science Board's efforts in helping to supply this kind of scientific expertise to other key FDA initiatives. In just my limited time here, we have benefitted greatly from your contributions to such critical areas as pharmacogenomics and more efficient mechanisms for developing new drugs and

demonstrating that new products, new medical products, are safe and effective at a lower cost and more predictably and in less time to quality systems for our own review procedures as we, like other people in the public-health system and in the healthcare industry, are working to identify best practices and spread them throughout our organization to efforts in critical path research in finding better ways to turn good scientific ideas into safe and effective products that people can count on.

So we thank you very much for all your support and all your contributions to these efforts. We are going to take another step in this process today. The entire purpose of today's meeting, the primary purpose of today's meeting, is to share our progress with you and to obtain your input on how to direct our food-security efforts.

You are going to hear from a number of different people, experts inside the agency and others. We are going to give you a number of challenging issues to consider and questions to

help us address as we continue these food-security efforts.

There is a broad agenda today to accomplish this goal and I hope that you will keep in mind, as we go through it, a few key questions, among others. First is the approach that FDA and our Center for Foods is taking balanced and appropriate. Are there any gaps in the program that we have outlined here and, if so, what are they and how can we best address them?

Third, are we devoting adequate resources appropriately in the various food-security-initiative areas? Are there any areas in which you would recommend a reallocation of our limited human resources or our financial resources?

Fourth, are the time tables that we outlined reasonable? If not, why not? Where might we better concentrate our efforts? How can we amend our priorities accordingly?

I am sure these are not the only questions that are going to come up as we review our food-security activities but I am also sure that your

insight on these and other questions is important because food security, itself, is not critical to our overall strategic plan, our overall strategic initiatives at FDA.

It relates to our commitments to consumer safety. It relates to our commitments to national security and domestic defense. It calls for efficient risk management. It calls for a strong and effective FDA. These are all, as you have heard before, key elements of our strategic action plan. In all of this, we also depend on better informed consumers and agency partners. So this is an integral program for our overall strategic initiatives at the FDA.

I would like to talk just a minute more about one key element in our strategic plan and that is better-informed consumers. I would like to thank those of you who are in the audience today who got up early in the rain to come out here to Rockville to hear and contribute to what we are doing today. We will appreciate your perspective as well. As you heard, there is a public comment

period later on in the meeting today.

We think we have been doing a good job so far in working together with our various partners in carrying out this critical part of our mission, with industry, with academic experts, with our sister agencies, with foreign governments and with the American public. But there is always room for improvement and we need to be challenging ourselves constantly to make sure we are keeping up and we are using our limited resources as effectively as possible.

In light of the complex food and health challenges that we are now facing, we really must be on guard to use the latest and best ideas about how we can accomplish our mission as efficiently as possible. That is why meetings like this one that we are holding today are absolutely critical for the future of the agency.

So I want to finish up by thanking you and, again, ask you for your best ideas and your help with the many urgent and difficult food-safety and security issues that we are facing today. As I

have said before, as I discussed with you last night, I think the public-health challenges that we are facing today are great. They are unprecedented. But also unprecedented are, as a result of scientific progress, the opportunities to make a positive difference for the health of the public, both in public-health protection and in advancing and improving the health of the public. These opportunities have never been greater as well and we need your help in matching up the opportunities and the challenges.

I am confident--I have been here almost a year now and I am confident that, by working together and using the talents and dedication of the staff of this agency, the willingness on the part of the many well-trained professionals at the FDA to always take a fresh look at what they are doing and always make sure we are adapting and adopting the most effective approaches--I am confident that we can, together, rise to the challenge of making sure that Americans continue to enjoy the best public-health protections in the

world when it comes to food safety and food security, food products that are not just diverse and fairly priced, but safe and secure.

I think you will also hear a little bit today about our steps to help make sure that foods are not only safe and secure, but also are developing and improving in ways that can help Americans promote their own health. We know more from nutrition science today and studies of obesity and healthy weights, about steps that people can take to improve their health, to avoid chronic illnesses, to live longer and better lives and we need help with that part of our food safety and security and health-promotion mission as well. Again, it is protection and advancement of the health of the public that we are most concerned about today.

So, in advance of today's discussion, I want to thank you. I look forward, after you have heard the presentations today, to our wrap-up discussions later on in the afternoon. Again, I really appreciate the time and effort that you all

are devoting to these critical public-health challenges with us.

Thank you very much. Do you want me to take any questions?

DR. DOYLE: Certainly. Thank you, Dr. McClellan. It's time for questions. Any questions from the Board? I guess you have awed us all so much that we don't have any questions.

DR. McCLELLAN: Let's get right to it. I think they are ready to get into the substance. Thank you very much.

DR. DOYLE: Thank you.

Next we are going to hear from Joe Levitt who is the Director of the Center for Food Safety and Applied Nutrition. Joe is going to give us an overview of the FDA's Food Security Program.

Overview of the FDA Food Security Program

MR. LEVITT: Good morning. It is a pleasure to be here. Apologies. I am glad I got here in time for my presentation. I apologize to the Chairman and to the Commissioner. It is a pleasure to be here.

We have, I think, a very interesting and exciting day. I want to thank Michael Doyle and the whole Science Board for your interest in this area. I thought we had a wonderful session yesterday afternoon to preview with some of the staff scientists some of the research that is going on.

I certainly want to thank the Commissioner who has brought such vigor and energy and vision to our program, not to mention a strong advocacy for our resources. I think it is fair to say that the $5 million that OMB allocated this past summer for research for food security would not have happened were it not for the personal intervention of our Commissioner. So we all thank you for that and for so much more.

My job today is to--I have the easy part. I am going to give you an overview to set the context so that the remaining speakers of the day will hopefully fit into the big picture.

We have basically three main messages. Number one, in the area of food security, there is

no doubt; we need to be prepared. This is a possibility. We all know that food can be a vehicle for contaminants that could make people sick or worse, that it could be used in a terrorist setting and it is our job to do the very best we can to be prepared.

Number two is that it has now been two years since 9-11. We are much better prepared than we were two years ago. While that is so, we still have a very long way to go. It is a kind of issue that the more you see and the more you understand, the more you see how much there is to do and what the scope of the challenges are.

But the good news is that we have not only made progress; part of that progress, and a very significant part of that progress, is setting out a blueprint on how to get there. So we feel we have that and we are ready and eager and moving forward.

This past summer, we sent a progress report to Secretary Tommy Thompson on food security. What I am going to do is outline what that is and that will, again, lay the background

for the remaining speakers of the day.

We started with four main principles. Number one, that food security and food safety are integrated goals. We talked a fair amount about this yesterday. We need to be building on the existing food-safety public-health infrastructure to fight the terrorism threat as well. We cannot afford to have what I think of as an "east is east and west is west" approach, safety is here, security is there.

We have strong systems. We have science. We have emergency-response systems. We have inspectors. We have scientists. We have research programs. We need to apply those with a new lens to look at food security in addition to food safety but also see them as interrelated. For many of these things, there are dual benefits as well and we need to maximize the synergy as much as we possibly can.

Number two, just like in food safety, the food safety and security system needs to be comprehensive. When we are talking about food

safety, we used to talk about farm to table, the whole scope of the food chain. We have to think about that here, too, but we also have to think about it more analytically in terms of how do you prevent, how do you protect, how do you do the full range of assessments and actions and preventions in a response. So this is a full soup-to-nuts program that we must have to be successful.

Number three, while the federal government clearly plays a critical role, we are not the only ones in this story here. This needs to be built on a solid foundation of truly national partnerships. All federal agencies, state and local agencies, private-industry consumers; this is a task that it so important and so big that it will require all of us working together in order to achieve our goals.

Finally, and this is I always feel important in almost every important thing we do; we have got to think of it from a consumer standpoint. We have to be sure that Americans have confidence in the government. A lot of times, I feel when we stop and analyze issues, we tend to see all the

complexities and all the steps and the potential barriers and funding and all that kind of stuff.

If you look at it from a consumer point of view, it is really quite simple; be prepared and take care of us and be honest and tell us what we need to do if something bad happens and, when you see it from that vantage point, what it really takes to provide confidence to American consumers. To me, that helps bring clarity of the other points. We have got to integrate food safety and security, build on our past successes.

We need to have a comprehensive system and we need to make that a truly national partnership and make this a truly successful program.

We then took that and tried to put it into thematic steps, thematic order. These steps are actually the main steps in the government's National Response Plan. So this is not something that the FDA brought up. This is our part of integrating within the broader federal framework.

The broader federal framework has five steps; awareness, prevention, preparedness,

response and recovery. First, awareness; you need to know what is going on. You need to not just provide information and raise consciousness but you have to get your information connections in there right. I am often quoted as saying, correctly, that when I first took this job six years ago, I never thought I would say, as Director of CFSAN, "We need a closer working relationship with the CIA." I couldn't have imagined saying such a thing.

But the fact is, it is an imperative now. And the fact is, we do, now, have a closer working relationship with the CIA and with the FBI and the whole law enforcement and intelligence community. So we have to get the awareness up. We have to know as much as anybody knows what is going on. There is now a large number of people in FDA that have security clearances at different levels and we have people at FDA that get regular intelligence briefings.

Number two, as with all public-health matters, prevention is always the best. Whatever

we can do to prevent the problem, to get out there in front of it and to catch something before it occurs, that is always preferable. The biggest advance FDA has made to date on this is at our borders. As I will get to in a moment, when 9-11 hit, everybody realized--I remember Secretary Thompson, particularly, resonated in a worrisome way, "What does it mean, we look at less than 1 percent of imports? What does it mean, we only had a few border around? How can that be? Does that look like a vulnerability?" And Congress did pass appropriations which has resulted in significant numbers of added people both at more ports and more people at existing ports. I will go through some of the results from that already as well as new legislation including better notice of imports coming in before they come in, so we can have a better prevention program.

Overall, three, preparedness. This gets into more the underlying infrastructure you need to have and develop an effective program. A lot of today's discussions are really going to be devoted

to that element of preparedness. What is the underlying expertise we need at FDA to make a good, strong FDA? What are the laboratory networks that we need. You will be hearing a presentation on that.

What is the research program and the research agenda to get the right scientific knowledge. We will only be successful--as with all of our important programs at FDA, our success is closely linked or tied to the science. We have got to start with the science to know what is going on, how we can be effective and how we can reach objectives that we need to. So preparedness, in a way, is the underpinning to everything else here.

Fourth, we know, no matter how aware we are, how much we try to prevent, whatever our underlying infrastructure of preparedness is, part of that is knowing, if something happens, we need to respond rapidly and clearly. So response is an absolute critical element. Is this something that FDA has a lot of experience with in general in terms of emergency response to foodborne-illness

outbreaks?

But we also know that, in the case of a terrorist event, it is going to raise the ante several levels up. There will be enormous media scrutiny. There will be enormous need to be able to respond almost instantly and that we will need to be out there with risk communication statements and information to consumers before we have all the information.

We like standing up there with the answer. We know there is a contamination in this food product. It is Lot So and So. If you have that lot in your home cabinet, take it out. It is being recalled. That is routine stuff. That is what makes us feel comfortable.

What do you do when you know there is a big problem and you don't know what the cause is and you don't really know exactly what is safe and what isn't. We experienced that with the anthrax-in-the-mail episode, by now almost two years ago. It is a scary time. But, nevertheless, again, think of it from a consumer point of view. They

don't want us to stand up here and say, "This is a scary time."

They want us to stand up there and say, "This is what we know. This is what we don't know. This is the best advice we can give you and we are going to keep updating you and giving you more information as soon as we possibly have it." So response is going to be not just the follow-up investigation but the public-communication aspect of that.

Finally, something that is, I think, all too often forgotten and it is the last thing on the list is recovery. As much as we try to be ready for response, we hope it doesn't happen, and so the follow-through. We have got to be sure, again, part of a comprehensive program. If there is something that happens somewhere, well, you don't want to shut down that sector of the world from time forward forever.

We need to have a recovery plan. How do you disinfect? Again, think of anthrax and the Hart Building downtown. EPA went in and had a

disinfection program. It took a while but people are now back there working and it is a functional building. So recovery is a critical part of all this.

Now, to address these five strategic categories, we put together a ten-point program that is more in what we think of as operational steps because so many of the things we do cut across these different categories. We found it easier just to think about it ourselves than to explain to others, to think of it in operational terms.

So we have ten operational categories. Number one starts with a stronger FDA. I already mentioned quickly that, with the supplemental appropriations following 9-11, FDA hired over about 800 people, 650 some-odd went to our field and the vast majority of those went to the border, both people at the border as well as people in laboratories supporting work at the border.

We have already seen results. First is in terms of taking a strategic approach on imports.

Step 1 was what I call narrow the gap, try to start plugging the hole and not have what appears to be a large vulnerability out there. So FDA has increased our presence from 40 ports to 90 ports and we are now at virtually every major port that imports food that we regulate.

We have increased the number of physical examinations at the border really at a staggering rate. Two years ago, we inspected, at the border, 12,000 food entries. You don't really know how many 12,000 is. But, two years later, this year, our number--we just got the numbers in is about 80,000. So that is a six-fold increase in what we were doing before.

It is still a very tiny proportion of the overall but, nevertheless, Step 1 established a presence, "Don't let this be the weak link." We are making good progress but we know we have to do much more. We know the imports has to be a broader strategic approach--part of that will be helped with the new Prior Notice Regulation which I will talk again more about in a minute--because it is

really going to come down to effective targeting.

Our job will be, no matter how many tens of thousands we can look at, there are millions coming in. The way I think of it is, with better targeting, we have to shift it from looking for a needle in the haystack to either having a magnet that pulls it out or at least be able to say which part of the haystack we have to look more intensely in. That is the goal we have to get to and we are working on that through all of our FDA-regulated products.

Number three is the new Bioterrorism Act Regulations. Again, in addition to the new money that was appropriated by Congress, Congress passed a major Bioterrorism Law. There were four major provisions in it concerning FDA that required regulations.

There are many more provisions that relate to a broader spectrum of activity, but the key ones are, number one, every firm needs to be registered with the FDA so that we have a full inventory of who is out there doing what. Number two, all

importers into the country, those five, six, main entries, they all have to tell us in advance what is coming in so we can put it through our computer triaging system and we can effectively target. That has got to be an absolutely critical part of our overall strategy.

Those two final regulations we just published on time the last couple of weeks. We were on kind of a breakneck speed time frame in that the law was passed and signed in June of 2002. We issued proposed regulations in the winter and spring of 2003, final regulations for the first two in October of 2003 to be implemented by statutory time frame on December 12.

So we came through and met that. We feel very pleased about that. In addition, there are two remaining regulations, one dealing with record keeping. So food companies will need to keep records of both who they bought it from and who they sell it to, what is called "one up, one down," so that if there is an outbreak, we can more rapidly trace what happened to the food, either

forward or backward through the chain,

Finally, there is a fourth regulation that is called administrative detention. So, if we do find a contaminated lot, we can actually hold it right there, pending the more complicated federal court action we are required to take. What has happened in the past is we would have to go to a state authority and ask them to embargo it while we go and do our federal court procedures. This gives the FDA the ability to do that.

As I said, let me go through the first two quickly that just became published. On food registration, what it will do is it will facilitate timely notification and response in the event of a food-safety threat. We will know where everybody is, who is the business and we will know what business they were in. So, if there is a problem with cheese, we can push the button and say, all right, we need to notify these people that make cheese.

If it is canned fish, we can do that. Whatever it is, we can find out where you are. We

have published an Interim Final Rule on October 10 with an effective date of December 12. It applies to most domestic and foreign facilities. There are exemptions. It doesn't cover farms. It doesn't cover grocery stores and restaurants.

The registration system is now operational. You can register--a company can register on line in about ten minutes. We have gone around and done demonstrations. I say that is probably the single biggest thing that has helped us, credibility with the industry, because a vast industry is a nightmare; oh my gosh, what is going to happen, how much paperwork are we doing do, how long is it going to take, what are the hassles when they lose it.

I have tried and I just get stuck. So we have an on-line system that went on-line on October 16. As of last count and last week, we already had 20,000 firms register. So it is moving. It is operational. There are a few glitches along the way, as you will have, but they have been able to get them rapidly fixed and continuing.

It is a one-time registration, not an annual, although companies are required to provide updates if they change the nature of the products, the business they are in, if they open a new facility somewhere and there is no fee associated with it.

We have a health line available that is 24 hours, seven days a week, and can be accessed worldwide. There is a part in our regulations that help you on how to identify food-product categories.

Prior notice of food imports. This one has been actually much more controversial. I think the registration system, once people understood, "I can do this in ten minutes? All right, I will do it." The prior notice has been much more worrisome because of the fear that essentially the FDA would shut down commerce. That these five, six main entries that come in--that is 25,000 a day--a lot of them come in over truck from Canada or Mexico. The fear, oh, my gosh, before we know it, the line will go from the Rio Grande all the way down to the

Panama Canal, and what happens then.

So there has been a lot of work here to work in a fully integrated way with what had been called the U.S. Customs Service, now is the Customs and Border Protection Unit within the Department of Homeland Security.

So, number one, companies can submit their prior notice electronically in a one-stop-shopping method. They can send it through the existing customs electronic interface that they are used to working with anyway. That has been modified so that it includes all the provisions that we need to have included. So that was kind of breather number one

Breather number two was that FDA had proposed notice noon the day before. Well, I guess we got people's attention with that. Then, afterward, the notion of, oh, my gosh; if they need that much time, they are not going to be able to work in real time. We didn't really know what the right amount was so we put that out so they have something to react to. We certainly got a

reaction.

But that has been modified again very substantially. I joke because it is a way to help me remember it. I am from New England and always grew up with Paul Revere, "One of by land and two if by sea." This is actually two if by land and eight if by sea, but it goes to a two-hour, four-hour, eight-hour, depending on the mode of transport. It is two hours if it comes in by land, four hours if it comes in by rail and eight hours if it comes in by boat.

I haven't heard such a collective sigh of relief since almost--you know, after the hurricane passes, whew, we survived that one. But, again, that resulted not only from listening to industry but working with customs on what really can happen.

We are also using new authority under the law to what is called commission customs employees to essentially be cofunctional with FDA as another way of expanding our work force and getting them to do a lot of the help at the border. We are also going to be housing more of our people in customs

facilities to be sure these computerized networks hook up. Again, we have got a single consolidated system.

These notices are required to be submitted electronically. There is no other way to do it. As I said, they have to come through the customs place. There are some exclusions for personal use; home-made goods, product regulated exclusively by USDA. They have their own system that takes care of that. This is not intended to do that. But these two regulations are the first main linchpins to do legislative authority helping us fight terrorism.

After we get that, I am going to run down rapidly because you are going to hear most of the stuff in more detail later in the day.

The fourth area to highlight is industry guidance for preventive measures. One of the very first things we did was companies come to us and say, "What can we do? What should we do? What do you want us to do? Don't make us, as an industry, thousands of companies, reinvent the wheel and pay

the same consultants over and over again for exactly the same information back."

So we have put together guidance and issued that in January, so it must have been January 2002, which was finalized the following year which laid out what I think of as a menu or a smorgasbord of activities that companies could consider in the area of physical security, in the area of personnel, in the area of control over products, management recalls, and so forth. That has been very well received.

We were asked to do additional specific ones, one for the retail industry on the principle that, if you think of it, if you are a food company, one of your goals is to keep strangers out. If you are a grocery store or restaurant, one of your jobs is to invite strangers in. It doesn't do any good to not let people in your business. So it presents a different dynamic, and so we have tailored a new one specifically for retail and a new one for cosmetics so we have the full gamut. Then we are starting to look at specific areas and

we issued guidance on fluid milk last June.

Vulnerability assessments; Bob Brackett is going to do a much more extensive presentation but I think one of the most significant things we have been able to do--again, going back to where is the strength. The strength is in the science. Where is the importance? The importance is in the strategy. You start with the science. You build a strategy. So we started with vulnerability assessments based on scientific principles--Bob will go through these--adding in what information we know about threats from intelligence sources and it has helped us very significantly winnow down where are the areas we ought to be applying our attention to with the most vigor.

That applies to how we focus our research agenda, how we triage methods needs in the laboratory, how we triage guidance to the industry. Everything flows from that. If you know your priorities, you know your strategy, you can roll. If everything is, oh, my gosh, what about this, what about that, you just kind of go in circles.

So vulnerability assessments is really, the, I think, key starting for a government program.

We also have to realize that there are going to be some times when we are at a heightened state of alert. We are all now familiar with a color-code system of red alert and orange alert and yellow and so on and so forth. One thing every agency in government has been asked to do and, I think, appropriately, is what happens, what do you do automatically when it goes up.

Some things you will see, like I know in the Parklawn Building or, I guess we are next to the Parklawn Building here, if we go up to orange alert, I can tell you, there are more security guards out there and they are checking more vigorously than they would if they are at yellow alert. That is an example of just something that automatically triggers in.

What triggers in with us, in addition to the things around our buildings, is increased scrutiny for certain kinds of products, again based on our vulnerability assessments. We implemented

that the first time during Operation Liberty Shield which was coincident in time by design, obviously, with the beginning of the war in Iraq. So we were able to ramp that up. That was both a learning experience but also an operational experience and we felt we learned a lot about that.

Again, our import program got sharpened up to these products, these areas of the world, and afterwards, you kind of go back down a little bit but try to learn, what do we learn from that. Again, you obviously are retooling and refining your priority-setting system.

Emergency preparedness and response; again, clearly a key critical area. Again, FDA has a lot of experience here but we are continuously--I don't think refining is the right word--we are continuously building and strengthening that through many exercises at many levels.

We have had an exercise just within CFSAN senior management. We have had exercises within FDA, within the department, with us and USDA at our level, with HHS and USDA at the Deputy Secretary

level. We have had a governmentwide exercise called TOPOFF-2 that I am sure you are familiar with and have read about it in the papers. So we are doing this intensely at every level.

I can tell you two things; number one, they are really sobering experiences because what happens is it goes through in very rapid fire. So you kind of live three weeks of hell in six hours. The three weeks have been bad enough. Six hours, you clearly realize how rapidly things can spin out of control if you are not on top of it.

So it is both sobering but it teaches you a lot. It also forges the connections between the agencies vertically as well as horizontally so that if there is an event, we are poised, we are ready. And we have some sense of what we would actually do in that situation.

The next two are areas you are going to hear just a lot, lot more about today. The first is laboratory enhancements. I think one of the real, if you will, light-bulbs going off over the last couple of years has been just the critical

role that the laboratory is going to play, not just in research but in response.

Following the anthrax episode, across the country, over the next month or so, there were over 100,000--well, like 150,000--samples taken across the country testing white powder to see if it was anthrax. Only a tiny fraction of that was in any of the states that actually even had a case. But you don't know how far it was spread. You had no way to track it and the labs were flooded.

We know, in our own building, and those of you who heard my last presentation, I won't go through the whole recitation, but we experienced that in our own building when we were down at FDA. We got our first lab result on a Sunday night that it was presumptively positive. But it was all the way until the following Saturday before we got a confirmatory negative. That was a week of pure hell.

We can't have that. We can't have a laboratory system that is so overloaded that you can't do the work. Again, think from a consumer

perspective. Consumers want to get it done. They don't want to hear excuses. They want action. And I don't blame them. I am a citizen and I want action, too.

So the importance of the laboratory, both in a cohesive and coordinated way but in a way that is trained for these kinds of agents. With biological, you start getting into BL-3-level laboratories and those kinds of needs, chemical agents provide their own challenges on how to do it. But, again, the laboratory is a critical foundational element for us to be successful in this effort, not only in response but also in surveillance. If we are going to start doing more surveillance here, which we will need to do.

Again, based on our threat assessment and priority scheme, we need to have labs capable of doing the work. The FDA lab systems are simply not set up to work on that order of magnitude. So working with all of our sister agencies and with a wide number of state health and agriculture department laboratories as well. You will hear a

lot more about that this afternoon.

Research; most of today is going to spent on research so I think all I will really say here is, again, the two light bulbs that were not obvious were one, how important the labs are. Usually, you think of FDA, you think of the inspectors or you think of premarket approval for new products and the laboratory is kind of like a background thing. The laboratory has got to be central here, but the research agenda--there is so much here that we need to know that we don't know.

There is a fair amount we know. But, as you look at it, these are agents that haven't thought about foods, a lot of them. We don't necessarily know what interacts with them, what kills them, what dose responses. We don't necessarily know the methods for the laboratory, what prevention technology could be effective.

So there is a whole scientific agenda that needs to be addressed. The initial money that will be provided, and this past summer is a good start. We hope it is a downpayment on what we hope in the

future will become a dedicated research program in food security. Bob Buchanan and others will be going through this in great detail.

Finally, you have heard me say this and refer to this throughout; interagency and international communications. We actually have exercises now involving Canada, involving Mexico and this will continue to expand. But, again, everybody is part of this network and there are intra-agency working groups on all these subjects. We have working groups on incident command and response, on laboratory preparedness, on protection steps, what we call shields, and there is, I think, an unparalleled level of collaboration going on across all of those.

We tried to take a step back and kind of say, you know, where are we? What are the needs? What we did here is, to explain the chart, we took the three middle areas of those five themes, prevention, preparedness and response, and listed some of the specific things that fall into each of those categories.

Then we looked at where were we in 2001. If 9-11 had been an attack on the food supply, how prepared would we have been? Two years later, where are we and where do we feel we can get to in 2007 which was four or five years out. Again, using the color-coded alert levels, red is bad. Red means we are at very high risk and very vulnerable. Green here is the lowest.

Basically, what this chart shows, if you look in the first column, if 9-11 had been an attack on the food supply, we would not have been ready for it. Essentially, you see red in every category except for emergency response, given that FDA has had traditional emergency-response systems but, again, not geared to the pace and intensity that we need.

Two years later, you see all of a sudden some of these are turning to orange. Our inspections are up. Our intelligence-gathering is up. We have come out with new regulations on registration and prior notice. We have improved our physical security.

But there is just so much more to do. Again, what our blueprint is designed to do is to get us from this interim step to really realizing what the magnitude of a comprehensive program is, how to make that again coincident with food safety and security together but a comprehensive program based on a national foundation that meets and responds to consumer needs.

Let me then just give a short preview of what the rest of your day will look like. The next three speakers are from my center, from CFSAN. Bob Brackett will talk about our threat vulnerability assessments. Bob Buchanan will give an overview of our research program. I will say, and we joke about this--there is a joke in CFSAN; if you want the big picture, talk to Joe Levitt but if you want the real substance, talk to someone named Bob. You have two of the finest here today.

In addition, we are happy to welcome David Armstrong who is from our Chicago research facility to talk about prevention research. We have a collaborative program out in Chicago at the

Illinois Institute for Technology, what is often referred as the Moffitt Center. We have there a pilot plant, a very unique laboratory facility. We are building a BL-3 laboratory there and we are counting on that program to do a lot for us in the future in the area of prevention technologies.

But then you are going to see this is not just a CFSAN program. This is an FDA-wide program. Dan Casciano will be talking about the important work that is going on down at NCTR in Jefferson, Arkansas. Dr. Linda Youngman from the Center for Veterinary Medicine will be going through issues relating to veterinary-medicine areas.

Carl Sciacchitano from Office of Regulatory Affairs will be talking about the whole laboratory network, what we are calling FERN, Food Emergency Response Network, and the progress that is being made there, to cover kind of the direct food but it is also, again, a broader FDA program.

Jesse Goodman, who is my counterpart in Center for Biologics, will be talking about the important work that the Center for Biologics is

doing, particularly in the area of vaccines. Diane Murphy, from the Center for Drugs, will be talking about important medical countermeasures. Again, when you think response, it is not just going and finding what happened. If you have got people who are sick, how do you treat them? That needs to be a critical and integrated part.

I think, too often, again we think food is here and drug is here. But it is all part, not only of the Food and Drug Administration, but it is all part of an integrated, comprehensive program.

So I think you have got an exciting day ahead of you. I will simply end where I began. Number one, we need to be prepared. That is our job. Number two, while we are much better prepared than we were two years ago--and that is clear; we are much better prepared than we were two years ago--nevertheless, we have a very long way to go to do this right.

We are not satisfied to be in the orange category. We need to be in the yellow and green category or we need to get there as smartly, as

systematically and as efficiently as we possibly can. At this point, we are fortunate that we have developed and do have a blueprint on how to get there and we are ready to go, not only ready to go, but we are off and running.

We welcome any and all input, feedback, that you have. These are new areas for everyone, a lot of them. And it is challenging to the mind, invigorating, but we also know we don't have a monopoly on good ideas. That is one reason we invite you and we hope why you are willing to dedicate a substantial part of your professional lives to helping us.

So we thank you for involvement and your advice and I will take a couple of questions if there are any.

DR. DOYLE: Joe, that was an outstanding overview to set the stage for today. I really do appreciate it.

Do we have any questions or comments? Yes; Dr. Pickett?

DR. PICKETT: Just a quick question. I

was surprised to see on your chart, in terms of time lines, that in-line detection technologies would still be orange by 2007. It seems to me that, as one thinks about being prepared, that that is a very important component, rapid detection and obviously having the lab capacity to do that. So I am curious whether or not that area is appropriately resourced to make certain that, perhaps, the time lines could be shortened.

MR. LEVITT: Excellent question. When Bob Buchanan is up here, you will see an overview of what the research priorities are. The reason it was listed that way is the belief, based on what we have seen so far on these biosensors and so forth, it is very difficult to get them effective in a food matrix. So that is the expectation that we have got, a several-year research program. It needs to be started now, but it is going to be longer before we get to where we are going to be compared to some things like laboratory methods that can be developed much more quickly.

So it is not a reflection of what we think

is the importance. It is a reflection of what we think is the time line to get that done and, as you will see, in any world, there are finite dollars and where can you get the most bang for each dollar that you put in. But that is simply why.

DR. DOYLE: That is an excellent point.

Dr. Riviere?

DR. RIVIERE: One very quick question. What happens on the prior notice on shipments if you don't follow prior notice and come to the Board? In other words, what is the teeth to this regulation?

MR. LEVITT: This is the way it works. Under the law, if they don't provide the prior notice, they don't get in, period. There is a lot of fear and understandable fear that--you have got so many thousands and thousands of importers. How is everybody going to get the message?

So what we are doing is we are putting in a transition policy so that, for the first four months, if they come in without it, they will get a feedback letter that says, "You didn't do what you

were supposed to do. We are letting you in this time. But this is what you have to do in the future." That will get ratcheted up, actually, over, first, a four- and then an eight-month period.

That is consistent with what we would normally do with new regulations. When we came out, for example, with the new seafood HACCP regulations, the first year of inspections, we don't take them to court right away. We give them a feedback letter; "This is a new regulation. This is why you need to do to comply. Next time in here, we are going to expect you to do it."

So there is a phase-in, so that there is a reality base to it. To us, December 12 is clear. But there is a big world out there. Not withstanding the fact that we are doing meetings literally around the globe--we had an international video conference--nevertheless, there are just so many. Again, working with customs, it naturally takes time for the word to get all the way through. So we are trying to phase it in that way.

DR. DOYLE: Dr. Swanson?

DR. SWANSON: First of all, I would like to compliment the agency on the prior notice and the registry process, listening to the comments that were made from the proposed rule to what came out, because it is more efficient and workable than the original one was and we are working through the system.

One of the things to look out for, and I think we need a creative solution, is we are trying to figure out how to deal with R&D-type samples that do come in across borders. It is one of those that really wouldn't have a huge impact on security issues because it is going from one research center that may be outside the country and in. We are registering our research facilities even though we don't need to because of this. We need to be thinking about how to creatively do that because we have got as many as ten or more a month that will be coming in and they shouldn't be tying up resources unnecessarily.

MR. LEVITT: Okay. Good. Thank you.

That is good feedback.

DR. DOYLE: Dr. Thomas?

DR. THOMAS: What sort of coordination might there be with USDA with regard to bringing in meat and other types of produce with respect to the new legislation?

MR. LEVITT: There is a lot of collaboration with USDA. You will see that they are a full partner in the laboratory network. As I mentioned, there is a lot of activity in emergency response. The actual system for meat is a little different and has its own system. The number of meat imports is a tiny fraction compared to what we deal with. So what we have made sure is we are not getting in each other's way. We are not duplicating anything. But that system was working fine so we are trying to do fine, also.

DR. DOYLE: All right. I guess that is all, Mr. Levitt. Thank you very much.

We are going to take a short break and reconvene at 9:30. I think it is important that we try to do that, be on time, because we have got a

jam-packed schedule. So, 9:30.

[Break.[

DR. DOYLE: We are now going to hear from Bob Brackett on CFSAN's activities in the area of threat and vulnerability assessments.

Dr. Brackett?

Threat/Vulnerability Assessments

DR. BRACKETT: Thanks, Mike, and good morning to everyone as well. Thanks to Joe for giving such a good, complete overview. I think that is very helpful and I think it helps put into context what myself and the rest of the speakers will be talking about.

What I usually do when I start these presentations, especially in the last few years, talking about food security, is start off with this particular slide which also lists our food-safety mission within FDA and that is reduce foodborne hazards to the greatest extent possible. It doesn't really matter whether it is an intentional agent or whether it is an accidental contamination. The goal is still the same and that is to protect

the American public.

To do that, the other question I get asked frequently, and this has been alluded to several times yesterday and today, is how do you sort of balance food safety and security and what is the difference in many people's minds.

So I have put together a sort of a schematic to sort of show what at least is my perception of our philosophy is and how this all fits together. At the core of everything we do, and this has been mentioned, again, too, is a reliance--and this is a necessity--a reliance on sound science. This relies not only on the traditional laboratory sciences such as microbiology, chemistry and toxicology but more recent sciences that also play an important role such as risk assessment. All of these sort of guide the direction that we do for protecting the public.

On that core of sound science, we layer another series of programs. We take advantage of the science to apply programs to protecting the

food supply. These are the usual sort of food-safety things we look, like good manufacturing practice, HACCP and the surveillance programs that we have or that we share with our sister agency at CDC.

Then, upon that, we have a third layer now which is the food security. These are things that we really never thought about before, such things as the physical security of the environment, of the production facility or of the transportation system, and the personnel who work in those systems.

We have always worried about in the past, or were concerned about, things like sanitation, easy accessibility to equipment so that it is cleanable, so that it can become disinfected, so we don't have accidental contaminants.

Now we are starting to say, is it too accessible? Does it make it easy for someone to get in there? So we have to balance, again, those sorts of issues with our traditional food-safety issues.

Joe already put this up. This is sort of the guiding framework that we are using now for all of the critical infrastructures in this country of which food is one, and I will get to that in a moment. But the point I am going to focus here again on is awareness because when you talk about threat and vulnerability assessments, that is kind of where this starts.

What I am going to do in this presentation is sort of give you the historical background, to put it all in perspective, so you know what we did, why we did it and when we did it.

If you look back in 2001, Joe showed the middle three of those items where we had all orange on the chart. With awareness, it was sort of the same. In 2001, we had very little awareness of the vulnerability of the U.S. food industry to terrorism. We knew about intentional contaminations and tampering but not of a thinking enemy actually trying to harm large numbers of people through the food supply.

We also had little awareness of the agents

of greatest concern. We were worried, and we still are, about Salmonella, E. coli-157, Listeria, the usual foodborne pathogens, but now we had a whole other range of both biological agents and chemical agents and radiological agents that we had to consider. These are things that we really didn't think about much before that.

We also had little awareness of the methods that we needed to detect agents in food. This has been mentioned before as well. Finally, as has been mentioned already, we had very little awareness of the characteristics and behavior of these agents in foods; that is, were they able to survive if they are biological agents? Were they able to infect a human being who would consume them. These are sort of things, questions, that we really had no idea at that time.

So the awareness part became very, very important in 2001 and it became our highest priority to develop what is known as situational awareness; that is, we needed to know everything and we needed to know it fast. Of course, that was

very confusing at that time because the problem was so big it almost seemed overwhelming.

We needed to know, first of all, are foods really that important in protection, or as an infrastructure. If they are, what are the most important foods? What are the things we really need to be concerned about and with which agents? Finally, what are we going to do about it? Ultimately, our goal is to protect the food supply. So that was another part of the awareness component that we were trying to attain.

To go to the first question about the importance of the food supply in this country, just a couple of different documents that have been released in the last few years. In 2001, the Department of Defense released a document, The Threat and Response Report, that, for the first time identified a tax on the U.S. food supply that could impact or affect the economic stability of the country and, in their interest, erode military readiness.

So, in fact, they, at that time,

identified foods in agriculture as a critical infrastructure. Then, most recently, just this past February, the White House, in the National Strategy for Physical Protection of Critical Infrastructures and Key Assets, designated officially foods as a part of the critical infrastructure. So it is important and it is recognized through the highest levels of the government.

So the question also comes now, at this point, since we have to know--we know that food is an important item. Why end up doing vulnerability at this time? As I mentioned, first of all, we want to identify the vulnerability to the food supply as a whole. Where are they likely to occur? Where can we put our resources?

Then, also, important to us, is to prioritize our efforts. As was mentioned, there is not enough money to do everything so we have to focus on those things where we are going to get the biggest bang for the buck. This includes guidance and outreach to the industry. How are we going to

identify to the industry, to the regulated industry and to the public, what things they need to be concerned about; our inspectional capability, so we can be more strategic in that level, and, as will be discussed more, the research.

Again, this includes methods, the characteristics of the organisms, whether they are even toxic in foods. There are some debates with some of these agents whether they are. On the one hand, they could be catastrophic. On the other hand, they may do nothing. But we have to know about that and then, again, countermeasures that we can use to protect the public.

When we started under the process of doing vulnerability studies for foods, there were a number of different ground rules or sort of philosophies that we included in the vulnerability assessments. First of all, we were interested in evaluating the public-health consequences of these agents and of the foods because, after all, we are a public-health agency, recognizing that there are other factors as well.

To do this, we wanted to be able to facilitate decision-making about resource allocation. Where are we going to spend our money that is going to allow the greatest prevention and protection and response that we can minimize the risk to the public as much as possible? Again, the thing that we were concerned about when we originally started this way back in 2001, and, as I will get into actually before that, was morbidity and mortality--that is, illness and death. They were the primary outcomes that we were considered with at that time.

We did not, at that time, consider other very, very important consequences like economic disruption, public alarm, public panic, loss of confidence in the food supply and the food industry. In some cases, these could be much more catastrophic to the nation than the illnesses and death could by themselves. So these, at that time, were not considered. Again, we focused on the public-health implications.

To get to actually where we did.

Actually, prior to September 11th, we had originally been thinking about this but not with the same degree of vigor that we did after September 11th. We actually had a contract with the Battelle Memorial Institute to do a vulnerability assessment with specific foods and agents. What they provided to us was a decision-making tool so that, in the event that there was ever an outbreak, we had a way, a logical way, to trace back to try to figure out what the most likely candidates were that were causing it.

After that, we took a much broader view. We did an internal vulnerability assessment within FDA and within CFSAN using a technique known as operational risk management which is a systematic tool for evaluating protective measures.

Just to give you a little bit of background about ORM, it is a logical six-step sequence that increases effectiveness by anticipating hazards and reducing loss. That sounds sort of formal and I will drop down, actually, to the bottom point. The origin of ORM

was actually with the military which is why these are stated the way they are. They were meant to protect airplanes on flight lines, to protect assets in the military.

We had an individual who was actually with the State of California Public Health who came to the Air Force at that time and adapted this Air Force tool for foods and it worked quite well. The purpose is to minimize risk to acceptable levels. It doesn't eliminate them. It just shows you where you should focus your resources to protect the resources as best as possible.

Of course, the benefits and the things that we were looking for was that it allowed us to prioritize our resources, our very limited resources.

These are the six steps that were used in that particular vulnerability assessment with the operational risk management. Step 1 was to identify the hazards that we were concerned with, and it is very food-agent-combination-specific, assess what the risks are, and I will get to that

in a moment, look at what risk-control measures we might employ, make decisions to actually do those things and then implement the controls. Of course, it is meant to be a circular logic; that is, you have to go back and look at what you have done and see if it matters and then revise if necessary.

When assessing the risk, it involved two components. One was the severity of an attack. It could range anywhere from negligible, minor disruption, all the way up to catastrophic. This means human illnesses. This means complete business failures. And there have been cases where this has occurred with natural contaminants as well. So the industry was aware of what this meant.

Then there are several levels in between, critical and moderate, each of which may or may not have catastrophic effects but still could have a catastrophic effect on the national economy if it was done in a large way.

Together, we compared these with the probability, and these are sort of subjective

probabilities, that this product could be contaminated with that agent. It could range anywhere from unlikely--and sometimes if you sit around at night and you think of all the different things that could happen, your imagination can start running wild and you can come up with some real theoretical sorts of things that could happen if you really stretched it. But, when it comes right down to practicality, you know that it is so unlikely that it is almost not worth paying attention to, all the way to frequent where we know that we have agents that have occurred in foods that has caused illness and death in foods and it could be added to foods again.

So, when you pair those together, you end up calculating a risk by combining the two. As I mentioned, you do a separate calculation for each agent and each food or activity. This allows us to separate the food, the agent and the activity into scenarios such as high, medium and low. So it is a coarse tool, but it is one that gave us a place to start.

There are a number of agent considerations that we had to include with this, one of which was accessibility of the agents. Some of the agents that could be used to intentionally contaminate food are easily accessible, either from laboratories or in the environment in many cases. Some are common household chemicals that could be used.

We also had to consider the public-health impact; as I said, morbidity or mortality. Is it going to be catastrophic or is it going to be more of a disruption. We also considered the toxicity if were a chemical agent or the pathogenicity--that is, if we knew, or if we could estimate as best as possible, what is the dose that would be required to cause a catastrophic outcome--and then compatibility.

Here is where the food technology and food science comes in together with the food microbiology or food chemistry. It is one thing to have an agent, and you could put it into a food. But, in many cases, we knew that it would not be

able to survive the processing conditions that would normally be applied to that food.

So we had to look at the ability to withstand processing. Or you could add it to a food and it would make it so foul tasting or smelling, no one was going to eat it anyway. So these are considerations that we applied.

When you do that, it puts it on a matrix that is shown here which, if you look at the severity, at the catastrophic, on the left and the top, and then the frequency, you would end up ranking that a 1. As you go matching the probability with the severity, you end up getting lower and lower ranks. So you have the red being the high risks, the green and the blue being sort of medium risks, and the white being low risks.

If you are dealing with a number of different foods, this allowed us to set up a priority ranking of where we were going to focus our efforts.

The results that we had gotten from the original internal assessment were very striking.

They were so striking that we believed, and also our upper management in HHS believed, you know, this is worthy of a second look to be validated. So what we did is we commissioned a team put together by the Institutions of Food Technologists which included food microbiologists, food chemists, toxicologists, forensics experts, both from the industry, from the government and from universities who had expertise and expect knowledge of foods including food processing.

So they knew things that we didn't because they knew where all the hidden skeletons in their plants were, to go through using the same foods, the same agent, the same process and they came up with virtually the same rankings that we did which was reassuring to us at the same time. But they also, since they had a little bit of extra knowledge that we didn't, identified some other vulnerabilities that we didn't. So that was very, very helpful and again solidified our ability to rank these hazards and then do additional consideration of them.

As I mentioned, the assumptions in these early assessments were limiting, that they only considered morbidity and mortality. And this was pointed out to use over and over again, but, from limitations of our resources, we didn't consider the economic consequences, public alarm, loss of confidence in the food supply or interruption of the food stream--that is, enough food--which, in some foods of limited quantity, that may be important.

So we were asked to put together some other tools that would look at these other consequences and integrate them in with the public-health concerns as well. That brought us up to our most recent type of vulnerability study which is known as CARVER + Shock. I will get to what that means. It is another acronym here in Washington.

This was commissioned actually by the Homeland Security Council at the White House and was put together with what we have as an interagency food working group which combined members of the Food Safety and Inspection Service

together with FDA-CFSAN food experts to go and employ this CARVER + Shock analysis to the high-risk foods that we had identified with the ORM procedure.

It was a little bit different than the ORM. Where the ORM was sort of a protective, almost HACCP-like in the way it was intended to work, this was something that the Homeland Security Council gave to us in that it was meant to allow us to look for vulnerabilities in the food supply. It was an offensive target-prioritization tool.

The goal here was to identify what are known as critical nodes that would be the most likely targets for a terrorist attack and then, again, to design shields. We wanted to protect the public, to reduce these.

So what we had to do is gather a group of experts for each of the foods and look at a very, very detailed schematic of the food-processing scheme including very minor points which might seem minor to the average person or even to us but, in fact, may be very critical in terms of introducing

an agent into the food stream.

The results, again, were very similar to what we had with ORM but provided much, much more detail as to where in the processing or distribution of that food we needed to focus our efforts.

The agency assessments that we had done within FDA and the ones that had done with Battelle were augmented because the process allowed us to identify not only the public-health significance but also the economic, psychological and political implications throughout the entire food-distribution system from, as Joe had mentioned, farm to table or to human, actually.

Just to give you a little background of what CARVER really is, it is a process that rates independently seven factors that affect the desirability of a target. The C is Criticality, the public health or economic impact; that is, if a person was able to introduce an agent into a food, what would the impact be? Would they be able to actually do something critical with that?

The second is Accessibility; that is, can they actually have access to a target. It is nice to be able to get it into the target, but do they realistically have a way to get it into the food. Recuperability is one that fits in with the part at the end of the five framework; can we recover. It addresses is this system, if it goes down, able to come back up or is that the end of that food company or the end of that whole system in the country.

Vulnerability is how easy it is to attack. The example I used is a bank vault. A bank vault is very accessible. We are allowed to walk in and out if you have the right key. It is not terribly vulnerable. The Effect is how much the direct loss would be to the company. For instance, if a lot of food was contaminated but it was stopped so that it didn't make anybody sick, what would the loss be to the company just because they had to discard that food.

Recognizability is an important part. Would a would-be aggressor be able to even

recognize what the target is? In some cases, it is easy and, in some cases, it is not so easy. And then the intangible part that was so important to this was the Shock part of it. This was a scored measure of the physical, health, psychological and economic impacts of an attack. Sometimes, that overweighted the public-health part of it, as I mentioned.

From this, we were able to get some very detailed analyses of specific foods and specific agents and it allowed us to then use that to drive other things that we are doing. If you look at the evolution of our Food Security Program throughout the last three years, you could see that in 2001, we started the threat assessments. We wanted awareness, looking at the foods and agents and then, from those, we have been going to building laboratory capacity and doing training and obtaining supplies and methods that we need to.

Then, through 2003, we were trying to find intervention methods to prevent the public from being harmed in case this would ever happen, or the

so-called protective shields. Much of what I will talk about will be followed upon by the speakers actually that follow me. So this sort of sets the stage for them.

So I guess what I will do now is just summarize by saying that the vulnerability and threat assessments that we have used and continue to use have allowed us to prioritize efforts. And that was a very important first step. They have been very, very valuable. We have acquired a very important vulnerability information which we have also shared with the intelligence community and law-enforcement community to put what they call the threat information; that is, what does the intelligence community think about our idea, what threats to do they know from the other side and how does that match up. So we are combining the two.

Both the food safety and food security programs are being directly influenced and, in some cases, driven by the assessments. They have been successful enough that we will continue to conduct and adapt these vulnerability assessments for all

of the FDA regulatory products of concern.

With that, I will stop. I don't know if there are questions now are later.

DR. DOYLE: If there is a burning question or a comment from the Board. I guess not. Thank you, Dr. Brackett.

Next we are going to hear from Dr. Robert Buchanan who is Director of the Office of Science at the Center for Food Safety and Applied Nutrition. Dr. Buchanan is going to talk about food-security research needs, priorities, resources and challenges.

Food Security Research Needs, Priorities Resources and Challenges

DR. BUCHANAN: As you might tell from my opening slide, actually, as I was starting to put this talk together, I was watching a Formula One race. So it sort of stuck in my mind. I thought it was very apropos because we have, during the last two years and when Joe mentioned it was two years almost to the day that we really scaled up to go to full time on this. It would be preceding

that. It was actually September 12, but really things started to fall in place.

It is hard to believe that it has only been two years. We have covered a lot of ground but certainly the race is not won yet. So I would like to follow up the same themes that Joe and Bob did, that we have come a long way but the race is not done.

So we would like to follow that up. I just want to reiterate, and also I just want to thank you from the scientists at CFSAN for coming over and visiting yesterday. Everyone thought it was a great visit and we appreciate you taking the time off and yesterday's afternoon to visit our new building.

I want to just reemphasize the fact that this is an area that builds on our past experiences but for which is one that we have had to have a new of thinking because it really does take a different mind set when you start to think about the intentional contamination of food.

When we have had those experiences with

tamperings and that is not unusual when you start thinking of things on a huge scale; that is, if you literally had an enemy that was purposely targeting your food supply, it really does take a different mind set. Certainly, a lot of our initial progress, we really sat down with a core group of people that were very familiar with the agents, with the industry, and literally sat around thinking about what would I do if I was going to contaminate the food supply.

We spent a great deal of time learning about that and looking at the consideration of new routes of entry, new agents that we might have to deal with and just developing that mind set for understanding. That is really the basis, Bob's discussion about the threat assessments and the vulnerability assessments and the priorities that were established as a result of that is something that I am not going to talk about a great deal, but it underlies all of the decision-making that you are going to be seeing as I discuss our research program.

I just, again, want to emphasize the fact that one of the reasons we were able to respond quickly is that we do have a good core of sound scientists and we do have a good strong research program that we can draw on. We have a lot of experience that is built up around that on our Food Safety Programs and then, taking this and enhancing it so that we are able to respond to a wider arena of threats.

I am going to start off by sort of going to the end and coming forward again. As we have looked at our vulnerabilities, as we looked at where we were in our state of knowledge, there are basically four priority areas that we have been dealing with and trying to address during the last two years.

I would like to go through those first so that you have an idea of what we are talking about and how we have responded to them. The first is knowledge of the agents. It basically falls into two categories. There is a great deal of knowledge of some of the agents. If it was a traditional

food agent, we have a lot of knowledge of those.

But when we started to deal with a wider arena of potential agents that could be intentionally put into a food, we started finding that, while there is a great deal of knowledge about some of these agents in certain contexts, there is actually very little known about them when you start dealing with foods.

This is even down to the basic oral pathogenicity and toxigenicity. Most of the agents that have been traditionally looked at for bioterrorism or chemical terrorism have been agents that have been examined in a different setting and in different routes of entry. So, for example, most of the information we have about the pathogenicity of a number of organisms is inhalational or cutaneous.

There is very little knowledge, in some cases, about what the oral doses are. Likewise, we have very little knowledge of what would be the matrix effects. We know from our own work with sort of more traditional pathogens that what food

you put an organism in can have a tremendous impact in terms of what is the dose that is needed to cause disease.

We have a great deal of experience in, for example, Salmonella knowing that if you put Salmonella in, for example, water, it behave differently than if you put it into a vegetable. It's different than if you put into a variety of other foods.

We also had an amazingly little information about some of these agents and their behavior in foods. So one of the questions as we went through, for example, earlier in our vulnerability assessments is what is the behavior of small pox in food and what is the behavior of a variety of protozoan agents, of a variety of viral agents. We really had very little information about those that we had to glean. We had to make some really quick decisions about where to focus our research but we still have questions because those are also--the behavior of those agents in foods is going to determine how we develop

protections in the food supply in order to be able to either inactivate the organisms, prevent their entry, et cetera or, in some cases, not worry about them because they just don't last.

The second primary area is then finding what is, in the jargon here in town, shields; that is finding ways of inactivating or neutralizing the agents in foods, in developing new technologies for putting an additional barrier up so that you protect them. It is also some security technologies, innovations in packaging. There are a number of innovations in packaging and inventory systems and forward and trace-back systems that are coming out that are very important in terms of how we would protect the product, some really innovative things like a hologram on the package that no longer is visible when you break the package in any way.

A variety of these are important research areas, also. I might note, these are some areas that are nontraditional research areas for us but it certainly came to the fore.

Then what I wanted to just highlight here is in-line sensors. There has been a lot of talk about these. You did see a prediction about how long it would take. For those of you who are not familiar with in-line sensors, they work really well in air. They work pretty good in water but when you start putting them in a liquid food, they tend to get really clogged up really fast.

If you are looking at big chunks go by, they don't work hardly at all. So it is a great basic technology and we are really looking for advances in that, but the reality is right now, if we have a hundred different agents we are concerned about, we don't have a biosensor that you can put in line that could detect it and last more than about 30 seconds. So we are looking for this as an important area.

Response and recovery; we are closely tying research here with our laboratory activities. Obviously, laboratory support is a critical element and something that we have been doing a lot of in terms of working with our field laboratories in the

FERN in order to get this up and running.

Rapid response research teams; what is a rapid response research team? I think the best example of a rapid response research team and the need for one is the fact that it is not just detecting the organism. Often, if it is a new agent, you have to solve a problem in a hurry. I guess the best example of being prepared is the recent SARS outbreak because that was critical not only identifying the epidemiology but identifying key laboratories that were able to do all of the basic research work in a matter of weeks and be able to solve an emerging health problem before it got out of hand.

Another response and recovery; this is one that we really didn't think about until we were in for a while and said, okay; we are sort of getting ready. Now, what happens if it actually happened? What would we do? What do you do with a food company after it has had an incident?

We had a lot of information--we were gathering information about detection methods, et

cetera, but we didn't have some of the basics like how do you clean up a plant afterwards. It is one thing--sort of the old adage is be safe or throw it out when you start dealing with food.

But you can't do that with a multimillion dollar food-processing plant. So one of the other areas we have been looking at is what do you do to assure people afterwards when you have had an incident that you have actually cleaned it up. Certain this, as Joe indicated, was a lesson we learned. We watched them try to clean up the office building next to us while we were still downtown and listened to the news and watched them try this and watched them try that until they finally got it. It took about six months.

Then, finally, and I have held this off to the end because this is the area that everyone thinks about immediately is detection methods and detection technologies. Actually, this is broken up into several different components. I have subdivided them so you can see the different areas really when we talk about methods. We are looking

for deployable rapid field test. It is critical, when you start dealing with literally hundreds of thousands of samples, you have to have a way of triaging samples so that you are able to get these looked at quickly, make tough decisions about which ones should go to the front of the lines, which ones shouldn't.

We found that, even there, you have to have some real capability of doing a higher level of analysis in the lab again for triaging, doing the screening samples, so that you eliminate or put to the back end of the line the 90 percent of the samples that are negative and really focus in on getting those that you need to look at first.

Laboratory-based confirmation tests; we need those--as we start dealing with a wider and wider range of materials, we are looking for multianalyte analyses both on the chemical and microbiological side.

We have learned a lot from the Bacillus anthracis case, the need to be able to go back and look at agents for attribution. So we have spent a

great deal of time looking at microbiological forensics and chemical forensics so we can also say and help work with the FBI and other law-enforcement agencies to determine who did it.
Really, that is part of the overall response.

Technology transfer always is a challenge. It certainly is a challenge as we are starting to work with large networks out into the field where we are dealing with networks of 100, 150 laboratories. How do we transfer the technology out? How do we deal with issues about not all labs have the same equipment?

We have transferring the technology when you are trying to keep certain aspects of your methods of analysis not widely distributed because the first lesson you learn is that if you tell someone exactly what you did in your method, that is the easiest way to give them a head start on figuring out how to get around it. I know, again, that is part of the thinking process that has changed.

And then, finally, methods validation as

we have developed these new methods, having a true comfort that when you put these out in the field that everyone will get the same result is something that we absolutely have to have. We also need to have a real understanding of the strength and weaknesses of all the methods and some idea of how they will perform.

We work real hard in getting the false negatives associated with these method down to as close to zero as we can. There are often tradeoffs in terms of speed versus false positives. Certainly, when you are dealing with complex matrices like food, the number of false positives that you get tend to be fairly large. The problem here is that every time you get a false positive, it overwhelms the system. So a high percentage of false positives means that everyone of those has to be confirmed and you can just tie up the lab for weeks. So we are trying to get that false-positive rate down.

So where are we and where are we trying to go? I am going to make a little pitch here for the

unique aspects that we do in terms of FDA research is that there is a great deal when we talk about counter-terrorism or biological research or chemical research--there is a great deal of basic research that is out there.

There is a wealth of information coming out of a variety of agencies, academic centers, et cetera. But it is our job to take that and get across the gulf that exists to safe products, sound policies, and guidance. To do that, we focus here within FDA on what we refer to as FDA translational research. That is that bridge that takes us from really good sound ideas and getting it out to where it is actually useful.

I just want to note this is a bridge. Under each bridge, you have a foundation that holds the bridge up. And, for us in CFSAN, it is an integrated research program that actually consists of three parts; our intramural program, which is a strong program that we can change on a dime if we have to; and extramural research program; and then a Centers of Excellence program. I am going to

introduce each of these a little bit more as we go along.

But, really, the bridge that we need to get to meet our mission is being able to take the good sound science that a lot of people are developing and translating it into something that is useful for the American consumer.

I might note, we have had some help along the way. I want to thank the Commissioner and all those that have been involved in getting us the $5 million supplemental this past year. It has certainly been something that has helped us get through the next lap. But I might note that $5 million is only a small part of the assets that we have brought to bear.

What really you need to consider and what we have done in the past few years is look at the fact that basically most of the resources we have brought to bear on this problem have been a redirection of existing resources. Within weeks of 9-11, we got all our scientists together, went through our initial thinking and, basically,

redirected 30 percent of our intramural research program and almost all of our extramural research program into this area as a critical need.

Having that capability and having the willingness of our scientists to do it really said a lot, to me, about the quality of our research program.

I might note that it was also the message that the Science Board gave us a few years earlier, this ability to respond quickly. I hope you see that, in this process, we listen to you.

I also am up here introducing the Foods Research Program. While my primary focus is going to be on CFSAN's internal programs for the rest of talk, I do want to indicate, and I will introduce briefly, the fact that it is a multicomponent research program that involves multiple centers and multiple activities.

These are the four major players in what we would consider the traditional Foods Program, though you will be hearing more about medical interventions, et cetera, later on. So, in

addition to the research we are doing, the Center for Veterinary Medicine, and there will be a presentation later by them; the Office of Regulatory Affairs, and they are going to be giving a presentation on the Food Emergency Response Network; and also Dan Casciano will be presenting the activities for the National Center for Toxicological Research.

Within the Center for Food Safety and Applied Nutrition, we do pretty much all four of those different activities, priority areas, I have outlined; methods development, agent characterization, intervention technologies and toxicity, pathogenicity, either directly or through our intramural-extramural activities.

The basic line that I want to reinforce over and over again is that we, wherever possible, attempted to get an addition not only to our Food Security Program but an addition to our Food Safety Program.

We have also tried, as much as possible, to leverage our activities and have been in contact

with a variety of other research agencies, academic settings. We have worked closely with the academic community and our sister agencies that support research are probably tired of seeing us be we have been very successful in working with groups like NIH, CDC, USDA research agencies and also DOD.

So let's, real quickly, just go through some of these activities again. I don't have time to go into individual projects and would be happy to give you details of any of those.

I did want to talk and start off by indicating the response that we had has also been very positive in terms of when you consider some of the barriers that we had to overcome, particularly in the microbiological side, and on the chemical side also. The first thing we had to do is really go back and sort of go to school because, while we were aware of many of these agents, I can't say that many of us had worked with them in great detail during that time.

So we had to learn to work with some of the nontraditional agents. We had to go through--and we

were under a mandate to upgrade our laboratory security. So, for example, not long after 9-11, if you were out to our Laurel, Maryland facility, it went from having a six-foot fence to having a fourteen-foot barbed-wire fence. Then we had to explain to the neighbors why there was now a fourteen-foot barbed-wired fence. Those are the little things you don't think about until you actually have to start doing them.

We had to upgrade some critical instrumentation and we did get a lot of support in doing this in terms of upgrading both in our research labs and our field labs so that we had comparable instrumentation. That is how I learned how many different mass specs people want. They come in all kinds of flavors now and so I learned more about mass specs than I ever knew in a very short amount of time.

Renovation of laboratories to perform at a BL-3 level. I have had experience with these. They are expensive. They are time consuming in getting up and running. This was, then, reinforced

with the recent changes in the select agent registration. I might note that all of our laboratories that work with these agents are in the process of being registered. In fact, most of our labs have been approved for this work now.

For those of you that are in that process, you know the millstone that you have to take to get that done. Our people have been really good about embracing these, understanding the critical nature of getting these approvals.

I did want to just point out--this is a picture of our Laurel, Maryland facility. This is where a lot of the microbiology work has been targeted. It was the first FDA lab to join the Laboratory Response Network. We have done a lot of work in terms of getting initial methods on the books, disseminating them through the LRN. We have done a lot of training of both the LRN and FERN members in analyzing for some of these agents and we have done a lot of work out there in evaluating some of the methods that are currently available.

Probably they are really tired of hearing

it from me, but, really, the mantra that we have had to keep it all in perspective is the word "what can you do if it is tomorrow?" That has really driven us, so we have taken a great deal of time trying to prioritize things so that we have something in place.

It may not be the most elegant method. It may not be the most elegant technology. But we had to first get something in place for each of the critical areas that we had. I am feeling much more comfortable now because I can say that, based on our threat assessment, we are 99 percent of the way there in terms of we could do something. Now we are really focusing on doing it better, faster, cheaper, more of it per day, et cetera.

One of the first things we did is not to rediscover the wheel. So the first thing we did is we got in touch with the military. We talked with the industry. We examined a variety of different sampling techniques, commercial facilities, to see what they had available and whether it would work in food.

Where that didn't work, we started developing our own. We have had some real ground-breaking work based on some of our past strengths in molecular biology and microbial genetics to be able to develop some really enhanced forensic work. We have been cooperating and, as Joe said, all of a sudden, we have a whole bunch of new partners out there.

We have been working very closely with the FBI, the CIA, DHS, DTRA, working with research partners that we have never worked with before. You did see a demonstration of some of the approaches that we are doing and being able to go back. We are not particularly focusing on anthrax on this. This is actually being done by another center that FBI is working with, but we are, in the area of enterics, really focusing on getting some really good forensics if we had to do attribution.

We have talked about biosensors. This is one of the biosensors that our people are working in collaboration with Cornell on. The question about, do they work. This works really well in

water. When you start putting milk through it, and you have a lot of bacteria in it, you get enough nonselective binding that it tends to foul after a while. But these are all things that are solvable. They just take some time.

So one of reasons that, in 2007, we are still in the orange. We think that getting this to work for a variety of foods is going to be a pretty tough developmental problem.

We have also been working with CDC and the LRN to try and do enough validation work in order to be able to make some recommendations on how we change our analyses. For any of you that are familiar with Clostridium botulinum toxin, the current standard for doing this is a mouse assay. That basically involves using thirty mice at a time to do an analysis.

At 100,000 samples per day, there are not enough mice in this country in order to do the analyses that would have to be done. Second, I don't know if even NCTR couldn't handle--you have enough? Okay. Is that a promise? So we have been

working very closely with CDC to come up with an alternate algorithm on how to approach bot.

This is one that we have been working with them. It is actually going through internal approval at the LRN. We feel now, with an ELISA that was developed one of the ORA researchers, that we are in a shape now that we could, for a terrorism event, actually go through and do most of the screening on an ELISA and then actually go into a mouse assay only for confirmation. This would drastically cut down the number of mice that we need so that certainly NCTR could handle it then.

We have a similar level of activity on chemical methods. I might note that the basic testing strategy is again we don't know exactly what is in the agent. We can maybe reduce it down a bit based on the symptoms, but we are looking at two-stage, a nonlaboratory rapid screening that we can do and we have seen a lot of--we have evaluated a number of ELISA techniques, lateral-flow devices, certain paper chromatography techniques that show a great deal of promise for triaging the samples.

Then, ultimately, you do need to have a system of confirming them. These are laboratory-based and we now have a system that we are quite impressed with where we can look at about 300 toxic chemicals at a shot. The ultimate goal is to be able to screen for about 3,000 in a single pass. Now, it is not the most rapid way of doing things but it is one that we have a great deal of confidence in. But we are looking for improvements.

Now, I might note, this is an extremely good interaction between the research scientists in CFSAN and our scientists in ORA in our forensic chemistry lab that have a lot of practical experience in actually investigating criminal activities. Between the two, we are working closely together to then get these methods out to our field laboratories and to members of the Food Emergency Response Network.

We also, within our mission, are considering radionuclides and what would happen if they were introduced into a food. We do have a

small research program in that that we are able to fund. This is taking place up at our Winchester Engineering and Analytical lab up in Massachusetts. This is one of the projects that we were able to fund with the $5 million supplemental that we got.

You will be hearing from CVM about their Animal Feed Safety Program. I am just mentioning this briefly as an introduction. I might note that they have an extremely good facility on food safety. Basically, they can manufacture, I gather, any feed that they want in small scale. So they have a really great facility out there to take a look at that. You will be hearing more about that shortly.

You will be hearing more from Carl Sciacchitano on the laboratory response network and the food emergency response network, our ability to respond in terms of an emergency and some of the activities that need to take place in getting that ready, particularly in the area of methods validation.

I did want to take a moment to talk and

introduce the Centers of Excellence concept that we work on. This is basically where we have attempted to set up research initiatives between industry, academia and FDA. CFSAN currently has three of them, one with our National Center for Food Safety and Technology at Summit, Illinois, in conjunction with the Illinois Institute of Technology; our JIFSAN consortium which is here at the University of Maryland and then the National Center for Natural Products Research which is in Oxford, Mississippi.

Each of those are a very active research component and this has been a model that we like where we house FDA scientists on a university campus and have them work on joint research programs of mutual interest.

In terms of our CT activity, most of this activity has been out at our National Center for Food Safety and Technology. This center specializes in food processing and food engineering and food safety in conjunction with that and they have some unique facilities Dave Armstrong will

talk about.

Certainly, we have focused a lot of our work on finding mitigation strategies at the processing level there and he will talking about some of these projects. Also, we will be telling you about the new BL-3-level pilot plant that we are building out there, a very unique facility. It is basically that you could run a food factory with a BL-3 environment.

Our extramural research program is a small but active component of our activities. It just reflects the fact, and we fully are cognizant of it, is the problems that we are facing in this research area are just too big and too important to try and do alone. We have used our extramural research program to get unique capabilities, unique expertise and unique facilities.

We have been able to fund some very specific ones. These are five of the ones that came out of the $5 million supplemental augmentation of our own internal funding and funding from ORA on extramural programs. You can

see from the title some of the key areas that we are looking at. This one was specifically targeted on detection methodologies.

We have also worked, as I said, strongly with several of our sister agencies. We have been working closely with NIH in looking for means for neutralizing certain pathogenic microorganisms and biologically derived toxins. We have worked with DOD trying to set up some research programs looking at dose response relationships for nontraditional agents. We have worked with several research institutes on, for example, enrichment techniques for some of the more nontraditional organisms.

We have been able to leverage quite well and work closely with our research partners in a variety of agencies again with partners that, if you would have asked us two years ago, we weren't even sure that they existed. Now we work very closely with them.

So what is the future? At least for CFSAN, it is to continue to address in a systematic manner the priority agent commodity combinations

that have been derived from our vulnerability assessments. We will continue to focus on those first working our way down them until we basically get everything in the green.

We will continue to be looking at these four areas as our four primary research needs, addressing each of them and we will continue to seek additional resources to accelerate this process, overcoming--looking for new opportunities to get the work done faster and more efficiently.

But the big key here, and I had to end with my race-car theme, is that we are looking to keep focused on the goal to make sure that we do cross the finish line in our goal to protect the consumer from terrorism via the food supply by keeping ourselves focused on the key translational research that FDA is most uniquely set up to do and has to do because, in many cases, no one else will, to assure that the nation's food supply is not only safe from accidental contamination but also safe from intentional harm.

With that, thank you, and if I can answer

any questions on specifics.

DR. DOYLE: Okay. We can take a few minutes if anyone has any questions or comments. Yes; Dr. Nerem.

DR. NEREM: Bob, you indicated earlier in your talk that, within a few weeks, not only was there a redirection of your intramural program but most of your extramural research program. I am just curious. My experience with extramural research programs is they are at least funded for a year or whatever. How did you so rapidly redirect that effort?

DR. BUCHANAN: We didn't just throw everyone that we had a research agreement with out the window. But what we did, and, in part, we got lucky on the timing because it was early in our extramural-project cycle that we were basically able to say, here is what our priorities were last year. Here is what our priorities would have been if there hadn't been a change. Throw those out the window. Here are our new priorities. The timing was great because it was right in the early phase

of us writing up the next RFA.

So we threw those out, started over, went through a quick evaluation of what our internal capability was, looked where we had some gaps and then really focused on those areas where the extramural--you can do this if this is a way of life where you have a lot of emergencies, you can stagger your extramural program so that you are always turning a certain number over. You can do it, like, twice a year.

That gets to be a little tough administratively. But, in many ways, we have a lot of flexibility with our extramural program because we can change it from year to year. Even though, once we have made a commitment, we usually make a commitment for three years. We don't have everything and starting at the same time so it is always overlapping.

Does that help?

DR. NEREM: Yes. I guess coming from a university perspective, many times these extramural programs may have students doing thesis research on

them.

DR. BUCHANAN: When I say "turn it over," we redirect the new money or the money that has not always committed. We are very realistic about you can't go back into a program and just cancel it partway through because it is a poor investment that way.

DR. DOYLE: Dr. Laurencin?

DR. LAURENCIN: Very nice talk. I have questions about your organization's priorities in terms of packaging, both in terms of, one, for instance, certain polymer-based packages may secrete catalysts or other materials into the food. Is there any analysis that is done in terms of the packaging that is used?

The second is just in terms of protection from tampering or changes in the packages from the time it goes out from the supplier to market and how do you detect changes either by purposeful or nonpurposeful changes that take place in the packages?

DR. BUCHANAN: Let me start off first by

saying that the approval of a new packaging material--packaging materials are considered food additives, anything that would leach out of them. There is a whole part of our agency that deals with it through our premarket approval. They are referred to, I guess, as indirect food additives.

If we need more detail on that, I would be happy to get you in contact with those that would give you the specific details of what are the premarket requirements before something is approved.

In terms of our counter-terrorism research and the importance of packaging, there we are primarily focused now not so much on the package being the vehicle for the agent, while it theoretically could, because the amount that diffuses into the food is so small. It is not likely that you could get a high enough concentration of a chemical toxin into the food to really cause much damage.

Potentially, it could be used for microbiological means. But the way most of these

films are manufactured and used in the plant, that is not one of those real likely scenarios.

What would be more important here is having active packaging that allows you to detect when the package has been tampered with or the product has been counterfeited. It is the same kind of thing, is there something that you can put on the package like there is on the new twenty-dollar bill that lets you know that that was a product that actually came from the manufacturer and not somebody else that had taken it, did something with it and then repackaged it. So that is a very active area and that is where most of our interest is in research is these new package security systems.

DR. DOYLE: Answer your question? Okay.

Dr. Thomas?

DR. THOMAS: I had a question with respect to your methods detection and development. You referred to on-line or in-line sensors. Are some of these compounds then programmed to go into a high-throughput type of assay? Is there going to

be a continuity there or haven't you reached that point yet?

DR. BUCHANAN: We are looking at a couple of different systems. There are some systems that are set up that periodically take a discrete sample, and take a look at them. In some ways, those are easier because you can actually put a wash step in to clean the sensor off.

The ideal one is to have a high throughput where the sensor actually is inserted in the product line. This is particularly amenable to liquid products, milk or juices, et cetera, where you would actually be detecting on a continuing basis the analysis. The problem here is that those, because you don't have a clean step, they tend to accumulate food or nonspecific bacteria or other agents. The useful life of those has been a problem.

So ideally what you would have is a sensor that stuck in that could detect a thousand different agents on a real-time basis and identify those. Certainly, one of the areas that we have

been looking at is some of the IR technologies to at least tell you something has changed even if you don't know what the agent is.

DR. DOYLE: We will take one more question and then we are going to have time at the end of all the morning presentations to have a general discussion.

Dr. Rosenberg?

DR. ROSENBERG: You mentioned industrial collaborations. Could you just kind of comment and expand a little further about how you go about identifying those, how do you put them place. What are the mechanisms that you guys use for setting up industrial interactions?

DR. BUCHANAN: We have several, some of them as simple as putting contracts out in terms of research contractors. Martin, can I hold you off because I think when David gets up and talks about the Moffitt Consortium, that would be probably the best way of doing it because that was a Center of Excellence that was specifically set up to do that. I think he can articulate some of the lessons that

have been learned on that.

DR. DOYLE: That is a good lead-in then to our next speaker who is Dr. David Armstrong. Dr. Armstrong is the Associate Research Director at the National Center for Food Safety and Technology at Summit Argo which is part of the CFSAN program. Dr. Armstrong is going to share with us some of the research that is being done to prevent food contamination, intentional food contamination.

Prevention Research

DR. ARMSTRONG: Thank you, Mike. I just want to thank the Board for having the opportunity to talk about our research program out in Chicago. We don't often get a chance to get this kind of a public viewing and airing. So I appreciate the opportunity.

Maybe I can start out by saying that we have a collaborative center that addresses food processing and packaging. If I can go back a minute and answer a previous question on packaging, we do have some non-CT projects that address in-line sensing on packaging. One of our projects, I

can go into this in more detail with you a little later, is on ultrasonic detection.

Another one we are just looking at now is looking at imaging to detect pinholes in packaging. One of the problems with these on-line sensing capabilities is that they are too slow. Line speeds in industry run so fast that you can barely see the can or whatever it is go by. So these things just operate to slowly many times. If you can route them off at certain times and use your detection method, then they work fine. So this is one of the issues that we are working with.

I just want to go back. I feel like the entire speakers this morning have been preparing for me so I thank you all very much. Look at the strategies for critical infrastructures and we fit into, actually, the preparedness bullet that Mr. Levitt showed a little earlier. I don't know if you noticed or not but there were a couple of red bars there, so I think this scenario we need to work on.

Also, in FDA's overall food-security

strategy, we are really looking at the bullet, and I think we are unique here, in developing the effective protection strategies to shield the food supply. This, to me, is an incredibly important area, an area that needs a lot of attention.

As Dr. Buchanan said, we are one of the Centers of Excellence for FDA. We are the Center of Excellence where the rubber meets the road, so to speak. We are not so basic out in Chicago but, boy, when it gets down to the nitty-gritty, we are right there. So we are one of these bridges and I would like to think we are one of the bridges to the real world and reality.

The food-security research needs; we really need to know how these new or unusual agents behave in foods. There are a number of characteristics of foods and things that are done to foods that can determine their survivability. We really need to look at this in terms of these new CT agents.

We are looking at specifically, at the National Center, inactivation and neutralization

technologies. We are really interested in what is the effect of the food process on these new or added agents. Can we expect to get some protection? Actually dealing with microorganisms and toxins in foods is not new for this industry. We inactivate toxins and deal with pathogens all the time in this industry.

True, these are new ones that might be introduced but this is not a new subject and certainly we have been working on food security for the history of the food industry, basically.

Again, in our ten-point program for food security, with our interface with the industry, we are in a good position to suggest kinds of prevention measures that might be effective. So we have a unique position here.

Let me talk a minute about these collaborative centers that Bob is talking about. The National Center is actually a consortium of government, academia and industry. We were initially focused on food safety. Now we are food safety and security. We have a research facility

there for cooperative research in new processing and packaging technologies, modification of traditional technologies.

We have had a long history and a lot of involvement in HACCP controls. We always have been looking at interventions in terms of what we can do to make the foods safer. At the National Center, we have been looking at new technologies, specifically, that might improve the safety of the foods. So we are in a good position to start working on CT types of research.

We are also a source of training, education and information and programs on food safety and security. We provide a neutral forum. Sometimes, you can discuss issues in a research setting that you couldn't discuss with industry so easily or with other elements so easily in another setting. So we are a forum where food safety and security issues can be discussed.

Why did we need a cooperative food-security consortium? In particular, FDA needs access to a pilot plan. We need to now about food

processing. Our mission is unique in some ways in this way. We need to have access to specialized laboratories. We need a specialized laboratory for pathogen and packaging research, a BSL-3 laboratory.

We need to have access to expertise that only research in this area can generate. In the case of public-health emergencies, we need to be able to provide facilities and equipment. And we also serve as a training facility for FDA states and other in the public-health arena.

Our objective are to be able to address key public-health issues, establish scientific competencies, keep dialogues going with industry and academia, transfer our technology to others in the consumer-safety area and provide research support during emergencies. So we intend to foster a scientific exchange with the scientific community and we have done that pretty successfully, I think, for the past fifteen years.

Our current collaborative research program deals with high-priority food safety and security

research. We arrive at this program collectively with FDA, industry and academic input. We focus on intervention and prevention strategies. Now we are focusing on CT and BSL-3 pilot-plant research and looking at new technologies in the process and packaging arena.

Since many of you probably will never get a chance to visit our facility, I took the liberty of including a few pictures here just to show you what our pilot plants look like, a lot of equipment that wouldn't fit into a traditional laboratory setting very well. We have the capability of manufacturing, on a very small scale, many kinds of food products there. Indeed, we do some prototype food products and specialized technologies.

High-pressure technology has been one of the areas that we have been conducting a lot of research in. This is very high-pressure technology, by the way, going up to 100,000 psi to inactivate microorganisms. Our programs really directly affect FDA programs. We can start with the food-safety issue, have workshops or symposia,

generate research, get industry interaction going. This eventually evolves into a knowledge base which may go on to provide for policy guidance regulations.

These should be two-way arrows; in other words, we can also go backwards on this chart and go from guidance back into a research-type situation where more knowledge is needed.

The participants in our consortium are FDA, the Illinois Institute of Technology, University of Illinois. We now have a partner in the State of Illinois and we are unique in that we have industry memberships. How we go about getting these industry memberships is through joint interests, joint interests where we perceive we have a need and they have a need. We try to get a dialogue going and generate a mutual interest which goes along with a mutual program.

So I hope that is not too short an answer, but we have a process of selecting research which focuses on trying to fish out what industry and academia are interested in as well. We use this as

a basis for establishing a dialogue. It is a pretty effective basis, I might say, because we seem to be on cutting-edge issues out there at our center all the time.

Now I am going to talk about our shift to preventative research at the National Center. We were, as Bob mentioned, in a good position to change some of our research focus to address some of these new agents that might be introduced to our foods.

I wanted to talk a little bit about the ongoing research that we have there first.

We have three ongoing projects. One is on the survival and growth of nontraditional pathogens in foods. As we mentioned before, there is really not much of a knowledge base on some of these pathogens and their behavior in foods. There are a lot of things that are going on in foods that may inactivate or neutralize these things. We need to know about these.

The second project is on the thermal resistance of microbial agents that might be

associated with bioterrorism. There we not only have the technical capability but the practical capability of checking the thermal resistance in common food-processing techniques such as pasteurization or extrusion of some of the other unit processes that might be used in the food environment or food setting.

We really need to know how some of our traditional food processing would affect these agents. This is going to help us greatly in our ability to assess what might be the impact of introduction of these.

Thirdly, we have a project on the evaluation of ELISA assays to detect botulinal toxins in foods, C. bot toxin in foods. It is not too difficult to make an ELISA kit commercially but how these kits react with foods is another story and what the meaning of the results is is also of interest. Just because you may get a reaction, you may not have activity. So we need to determine if ELISA-kit activity translates to biological activity.

We need to know what the impact of the food and the impact of the process is on this assay. So it is a much more complex situation than one might think at the outset.

Just to into a few details on some of our projects. On the survival and growth of nontraditional pathogens in foods, we have been working with agents that do not require a license. Until we can get a select agent license for some of these things, we need to work with agents or organisms which are surrogates. Our objective is to determine if the agent that might be introduced will survive, grow or maybe die off in the event that they are added.

We have very little data, really, on how some of these agents might behave in foods. The benefits would be that we could probably help answer the where and when in a case investigation. We really need this information to make risk-management types of decisions within the agency.

We are finding that some of these agents might, indeed, be poor growers in nutrient-limited

foods and we are also finding what is good news that some of the virulence agents that might contain virulence genes die off much more quickly. So that is about all I can tell you about our results until they are declassified, I guess I should say.

We plan on continuing this work and eventually going into more select agents in this area; that is, agents where we can get appropriate license. We are going to look at other shelf-stable foods, things like infant formula, juices, sports drinks, et cetera.

The second project we are looking at is the thermal resistance of nontraditional microbial agents such as C. bot toxin--this certainly won't be the only thing we look at but this is one that we can talk about--and look at, perhaps, a combination of the effects of heat versus pH salt and a number of other parameters in the foods.

Again, we have very little data on how, say, something like C. bot toxin might behave and react as it goes through food-processing kinds of

operations. This, again, would be used in risk-management decisions.

A third area, actually, this was a natural because we actually had started this as a collaborative project before the CT era hit. So we are looking at these ELISA assays and can they detect botulinotoxin in foods. We have investigated food additives that might interfere with ELISA performance and we are also going to be a part of the Liberty Shield operation that goes on.

In terms of new research, we are just starting. We want to look at the effect of thermal and shear food process that might inactivate protein toxins and also, then, sort of then jointly with this project, looking at the decontamination of food-processing facilities and equipment. As Bob said, if there is an incident, it is not likely that you are going to bury the food plant along with the food. The food plant is going to continue to sit there. We may sterilize the food and landfill it, but we are certainly going to have to

do something with that equipment.

Looking at the first project, effective thermal or shear in food processing, we know that many proteins can be denatured by mechanical action. As an example, I would use egg white, whipping of eggs to make a foam. Food processes such as extrusion, foaming, homogenization where you have very high shear conditions, may inactivate or at least partially inactivate these toxins. We are going to look at combinations of processes.

Toxins such as C. bot toxin, ricin or fungal toxins or others might be investigated depending on where our risk analysis takes us. In all cases, we are going to attempt to correlate our biochemical assays whatever they are with actual loss of biological activity. We realize, from our past food knowledge, that, particularly on our projects with allergens, we have to look at the behavior of these ELISA test kits and how valid they are in terms of allergenicity and actual biological activity.

We are not going to lose sight of this in

our processing studies. We know, for example, that if you take C. bot toxin as an example, the toxin is still there after you process it. You have just inactivated it if you thermally treat it. So we are aware of this and we want to make sure that we are actually following biological activity. That is for the biochemists in the crowd.

The second project I want to talk just briefly about is the decontamination of food-processing facilities and equipment. This would aid a rapid recovery after a bioterrorism incident. We know the food would be discarded, but the facilities and equipment would not be and something would have to be done with them.

We need to know if the currently used food-sanitation techniques are effective. Again, sanitation is not anything new in the food industry. We battle pathogens every day but some of these are new kids on the block. We need to know how currently used sanitizers would work in this arena.

This project will be coordinated with our

previous project. While we are investigating the effects of our processing on these agents, we can also look at decontamination of the equipment.

I wanted to talk a little bit about the build-out of our BSL-3 pilot plant and laboratory. In order to conduct pilot-plant-related research on these agents, we are going to have to have some unique capabilities; that is, we are going to have a BSL-3 pilot plant and we are going to have to meet the select agent requirements of the Patriot Act.

There are BSL-3 laboratories around the country but I don't know of too many BSL-3 pilot plants and I don't know of any that are BSL-3 and meet Patriot Act requirements. So we have got our work cut out for us. We would like to be able to readily transfer select agents between the pilot plant and laboratory that we have and we realize that we are going to have much more stringent personal protection measures than we have been used to.

As Bob showed, this is a schematic of a

pilot-plant and laboratory design that we have been working on. One of the things that we have evolved from sort of our design research that we have been doing on the pilot plant is that we need to have an equipment decontamination chamber or possibly we could move equipment in and out of the pilot plant without fully decontaminating the pilot plan.

A full decontamination of any facility is really a chore and requires a lot of verification and validation. If we could move in enough equipment, that would aid our research a great deal. Also, we need pretty effective personnel decontamination means and we need to accomplish all of the safety and security requirements that go along with a facility like this.

As I said, this BSL-3 pilot plant will have restrictions particularly in handling select agents. So we have to meet all the requirements of the Select Agent Act.

This shows some of our old I will call it BSL-2, BSL-3, pilot-plant activity that we have done in the past. Here we are making cheese that

is inoculated with a pathogen. The personal-protection measures that we will have to accomplish with this new facility are even greater than this. We will probably have to go to bubble suits that are self-contained, so this is going to be a challenge.

The kind of equipment we might be using in our pilot plant is shown here. This laboratory food extruder on wheels we may be able to wheel in and wheel out and investigate food processes.

Some of the other equipment potentially put in our pilot-plant facility.

I just want to end with some of the hurdles that we are facing with CT research. We know we have to do, and we are involved in doing, a lot of security upgrades, as Bob mentioned. We have a lot of laboratory upgrades we need to do. We have more requirements in terms of select agents. We are getting a number of security audits from other agencies now. Here we are, FDA being inspected by other agencies.

We have personal background checks that we

have to deal with. Finally, in terms of collaboration, we are getting a mixed industry response. Some of our industry is just not that interested, apparently, in the kinds of CT work that we are doing. So I think we will continue to try to convince them that what we are doing is going to apply to food safety ultimately as well, and we are trying to bridge between food safety and food security such that we can apply the things that we learn in food security to food safety. So I don't see it as an isolated effort.

So, with that I will stop and ask if there are questions.

DR. DOYLE: Very good. Thank you. Do we have a pressing question or comment? Dr. Nerem?

DR. NEREM: Just curious. You talked earlier in terms of participants, industry members. And then, at the end, you talk about industry collaborations. Is there formal industry membership in the Center?

DR. ARMSTRONG: Yes.

DR. NEREM: Do they pay annual dues?

DR. ARMSTRONG: Yes; they do.

DR. NEREM: What is the nature of the relationship?

DR. ARMSTRONG: Yes; there is industry membership and they do pay what we call membership dues. We have several levels depending on--I don't want to go into our sales program but we have several levels of industry membership depending on their interest.

DR. NEREM: In addition to the membership fee, do they provide other financial support for research?

DR. ARMSTRONG: Yes.

DR. NEREM: Or is it in-kind?

DR. ARMSTRONG: Yes, yes. For example, we have a high-pressure unit there. I think to buy one would be in the neighborhood of $1 million. That was donated so that we could conduct--in fact much of the equipment that you see out there has been donated. So, yes; this is a very natural place to do industry collaboration. Industry is interested in where the rubber meets the road as

well and they are interested in the process aspects.

DR. NEREM: Do they get any intellectual property rights?

DR. ARMSTRONG: It depends on how the project is structured. I can be structured such that they can do--with IIT, not with FDA, even proprietary work. But they can sign agreements amongst themselves and do multiclient non-FDA-involved research. So yes; there are a number of avenues whereby they can investigate things there as well.

It makes a lot of sense to share the costs of bioplants. They are very expensive things to own and operate.

DR. DOYLE: Good enough. Thank you, Dr. Armstrong.

Next, we are going to hear from Dr. Daniel Casciano who is the Director of the National Center for Toxicological Research at the FDA facility in Arkansas. Dr. Casciano is going to address food-security research at the Center.

Food Security Research

at the National Center for Toxicological Research

DR. CASCIANO: Thanks very much. I would like to thank Joe and Bob for inviting me to participate today in this great discussion on food-security efforts at the FDA.

I thought, though, that prior to directing my attention to the food-security research at the NCTR, I would present you with a little bit of information who we are. The last time that I addressed the Science Board it was during the Kessler administration so it has been about five or six years. So I thought I would just put in a couple of commercial slides for the NCTR here.

This is an aerial photograph of the NCTR. I was hoping that John Taylor would be here so that he could see the new addition to our campus. This is the Arkansas Regional Laboratory here. This was dedicated a couple of years ago and it is collocated with us at the ORA, the Office of Regulatory Affairs. The Southwest Region has their chemists and microbiologists in this particular

group. We have started collaborating with them to a high degree.

This campus is now called the Jefferson Labs of Arkansas. That includes both the ORA and the NCTR.

Our mission here is described on this slide. It is to conduct peer-reviewed scientific research that supports and anticipates the FDA's current and future regulatory needs. So we have the luxury, we feel, at our institute, to do some long-term thinking that our colleagues in the regulatory centers don't have that particular luxury. So we feel quite gratified that we are able to interact with our regulatory scientist colleagues and participate in development of both translational needs and applied needs of the agency.

This slide gives you some idea of our organization and the various "ology" groups that we have. We have a biochemical toxicology. We have a very good statistical group, biometry and risk assessment, that also houses our toxicoinformatic

group. Chemistry is state of the art. This group houses our new proteomic and metabonomic activities.

As mentioned earlier, we do a lot of rodent research and testing so we need an excellent veterinary-science group which we do have. We have an internationally recognized molecular epidemiology group and a well-established neurotox group. Our microbiology group has two functions. They have a diagnostic and surveillance function as well as a research function.

It is the microbiology group and the chemistry group that are participating in our food-security research directed to agency needs. Our last division is genetic and reproductive tox. This group houses our core microarray facility.

Two years ago, we instituted several Centers of Excellence which include our Functional Genomics Center which is our core DNA microarray group that supports all of the hypothesis testing at the NCTR that utilizes these tools. And we have a Structural Genomics Center that is associated

with our molecular epidemiology group that is interested in polynucleotide, single nucleotide polymorphisms in the human population and they are directing their efforts toward understanding susceptibility of the population to various cancers.

Our ToxicoInformatics Center houses our bioinformatics group. We have a strong bioinformatics group that supports the genomics, the proteomics and the metabonomics efforts. We were quite fortunate in recruiting several highly skilled and practiced individuals in the specific area. This is the glue that allows us to interpret the reams of information and data that are developed though these processes.

This group recently developed a database, data-mining tool, that is available to all of the FDA. It is called the Array Track. If anybody is interested in obtaining that for their microarray analysis, they can contact me and I will make sure they get it.

As a response to adverse events, we have

developed an Hepatotoxicity Center. Several years ago, we developed the Phototox Center in collaboration with the NIEHS through the National Toxicology Program. This group supports needs, primarily needs of CFSAN in their cosmetic efforts and NIH compounds that have been developed through the National Toxicity Program. We are utilizing that system to a variety of dietary-supplement work as well in collaboration with CFSAN.

So the outline of my talk is I am going to give you a brief description of our BSL-3 laboratory. As all of you know, after 9-11, there was a paucity of BSL-3 facilities that were available to help in terms of catastrophic events. So the NCTR was provided funds to renovate a laboratory to maintain that kind of action.

I will tell you about the work that has been going on for several years. In the Microbiology Division, we view the counter-terrorism effort as the flip side of the Food Safety Initiative efforts that have been ongoing for several years at the NCTR and tell you some of

their DNA-based tools that they have been developing for detection methodology.

Recently, we have decided to direct some of our activities to develop proteomic tools which will allow us to speciate bacteria and also support other activities at the NCTR. This effort is located in the Division of Chemistry.

So the BSL-3 lab, the update on this facility, the contract has been awarded and we expect a completion date of summer of 2004. We are renovating a laboratory that was a BSL-3 lab about fifteen years ago and it was not maintained. We are renovating that space to now include seven suites for research and testing of a variety of select agents. It is in this specific area that we collaborate with our on-sight colleagues in the Arkansas Regional Lab that are associated with ORA. Hopefully, we are interdigitating with them. They are participating in not only the testing part of our activities but also in helping us develop research methodologies.

Another occurrence that we have utilized,

the supplemental dollars that we received through the counter-terrorism effort, we purchased individual ventilated cages to house rodent-model systems. These are very useful adjuncts to our efforts. We can utilize these systems in BSL-2 laboratories as well as in BSL-3 and these systems will house rats and mice, and we are now beginning an effort with Cryptosporidium parvum that is a collaboration with the EPA and our first experiments using these cages.

So now I am going to switch to the Microbiology Division and then I will tell you something about the efforts that are going on in the Chemistry Division. Our microbiology group has been quite active in the food-security and counter-terrorism effort for the last five or six years.

The next two slides are titles of projects that are ongoing in their group at the NCTR. The first one is the development of a microarray chip for the detection of multiple antibiotic-resistance markers. This activity was derived early on in a collaboration with the Center for Veterinary

Medicine.

We and they were concerned about antimicrobial research in poultry populations. Northwest Arkansas, I think, is a capital for production of poultry. That is where Tysons is located. We have been allowed to go to certain of the farms up there to obtain excreta from the poultry, both chicken and turkey, to attempt to isolate bacteria that are resistance to the antibiotics that they are given.

A second protocol that is being developed are novel molecular approaches for detection and analysis of the most populous bacteria species in the human gastrointestinal tract. Carl Cerniglia, who is the Division Director in microbiology has been interested in human gastrointestinal microflora for many years. He and his group has developed an in vitro system where they can identify the bacterial population in that in vitro culture system as well as understand perturbations as a function of exposure to either antibiotics or dietary supplements or whatever.

CVM has had a great interest and we have got a collaboration with them on the study of mechanisms of fluoroquinolone resistance in Salmonella species that have occurred both in animal feeds as well as in excreta.

There has been a recent use of competitive-exclusion products and probiotic products. We have developed systems that will help us understand the nature of those products and the relationship that the products would have with the host. We have developed in vitro models and in vivo models.

There has been a real concern about vancomycin resistance in these poultry samples. We have developed molecular-screening methods for determining that resistance and in vitro assays for perturbation of colonization resistance by antibiotic residues, et cetera.

We have a large study going on this, studies for fluoroquinolone resistance in Campylobacter species, especially those isolated from turkey. Evidently, there are those species

that are associated with turkey that are not very well characterized and the group in microbiology are expending quite a bit of effort in doing that. They also have a collaboration with the Chemistry Division which I will get into later on in the talk.

As I mentioned earlier, the division has two responsibilities, one of making sure that the animals that we raise and use for GLP tests are pathogen free. So they have tremendous expertise and experience in diagnostics of a variety of animal pathogens. So we utilize several techniques that are depicted on this slide and they range from biochemical techniques to molecular biological techniques.

The relevance of this group to safety and security issues are depicted on this slide. They have a tremendous amount of experience and expertise in diagnostic, in microbiology and microbial identification and experience and expertise in the use of automated systems for identification of these species. They have

expertise and experience in BSL-3 laboratory functions and operations which is very important for when our dedicated facilities come on line.

The reason why I included this slide is that these individuals who are not at presented dedicated to the counter-terrorism efforts are available in case a catastrophe occurs and we can redirect these individuals who have expertise to provide us with the necessary support.

Some of the research methods that are used in the Microbiology Division are depicted on this slide. They range from somewhat simple tests like disk diffusion and somewhat now considered traditional molecular technology like pulse-field gel electrophoresis and PCR to DNA sequencing and to DNA microarray. I will tell you a little bit about the efforts that are going on in some of these technologies.

One of our investigators had isolated a Salmonella typhimurium antibiotic-resistant culture and was interested in determining the virulence markers that were associated with this

antimicrobial-resistant bacteria as well as antimicrobial-resistant markers. So he developed this microarray assessment so that he could then identify more than 25 genes that were associated with this multi-antibiotic-resistant strain.

So this technique is a much more rapid technique in comparison to the PCR techniques that they were using previously where they would evaluate one gene, a single gene, at a time.

As well, as I mentioned earlier, we were interested in characterizing fluoroquinolone-resistant strains of Campylobacter that are isolated from turkeys. This is a slide projecting pulse-field gel electrophoresis fragments where one can identify and characterize the various strains using these specific restriction enzymes.

Then, again, they have developed multiplex PCR techniques which can also discriminate various marker associated with specific strains.

I mentioned earlier that there was an in vitro intestinal model that was developed. This is a function of coculturing a variety of bacteria

populations with an intestinal mammalian cell in culture. The investigators are using this to test the efficacy of competitive exclusion products in evaluating the antimicrobial drug-resistance transfer and detecting pathogen effects on intestinal ecology and they are attempting to study innate immune responses to intestinal bacteria.

Secondly, the have an in vivo model, a germ-free mouse model, where they are testing the efficacy again of probiotic products and evaluating the antimicrobial drug-transfer immune responses and pathogen effects. So they are comparing the in vitro model with the in vivo models that are available at the NCTR.

As I mentioned also, there is a large interest in the artificial human gastrointestinal tract. This slide depicts the most representative bacterial species isolated from the health adult human gastrointestinal tract. We have probes for all of these and you can see, on this particular DNA microarray--we can identify 40 of the predominant human intestinal bacteria.

We use this technique to look at perturbation of the populations. The populations are very complex. However, they are very stable so we can determine whether or not specific antibiotics or dietary supplements or chemicals affect the ability of those populations to thrive.

Here is the basic problem. It is not unexpected. Here is a microarray depiction of 11 normal human fecal samples. You can see that there is quite a bit of heterogeneity. So this is where we need to integrate our informatic tools and our statistical tools to help us normalize the data from one human to another.

The future research depicted on the next two slides is the continued application of microarray chip in detecting antimicrobial-resistant markers and foodborne pathogens in bioterrorism agents. We have a need to understand the role of the various genes in resistance development and development of microarray methods for detecting Salmonella species and Vibrio species in seafood, studying the intracellular signalling

mechanisms in mammalia cells by foodborne pathogens, especially the ones that are mentioned here.

We are developing baseline data that may provide information on development of quinolone-resistance in chicken and turkey intestinal microflora, continue to monitor using pulse-field gel electrophoresis profiles and the relatedness of bacterial DNA isolated from poultry and human sources, evaluating the contribution of probiotics towards resistance of foodborne pathogens--we think this is a real problem--and continuing to collaborate with our investigators in the Division of Chemistry whose activities I am going to transit to now.

In our Division of Chemistry, the main goal there is developing detection methods. We are directing most of our activity towards rapid bacterial characterization by mass spectrometry. You see here the tools that we are using. We are using pyrolysis mass spec and MALDI Tof mass spec in conjunction with pattern recognition.

These pattern recognition algorithms are those that are available commercially as well as those that are being developed within the Division of Chemistry. You can see the strategy of each of these tools. In the pyrolysis method, to heat bacteria and then distinguish bacteria by patterns of ions from all biochemical constituents while the MALDI Tof uses a laser to ionize the proteins and distinguish the bacteria by patterns of protein masses and, perhaps also, by the quantity of protein that each of the bacteria produce.

This is a slide of the two tools. You can see here that the pyrolysis mass spec has a much smaller footprint which makes, in the words of my colleagues who are doing this work, it somewhat portable where you can see the MALDI is certainly a laboratory-based instrument that is not at all portable at the present time. It also gives some information regarding the development of reproducible spectra, the number of cells that are needed to produce each spectrum and the amount of time it takes to obtain a spectrum. So it is

fairly rapid identification of protein spectra.

At the present time, our current major issues and questions are comparing the pyrolysis mass spec to the MALDI mass spec. We are evaluating the time of time it takes per sample, the specificity, the reliability and the practicality and, of course, the unit cost per analysis.

We are using as the standard the typical microbiological standards. That includes the PFGE and serotyping and antibiotic resistance profiles. The organisms that we are working with presently are shown on this slide. In addition to the hardware analytical development, we have two patent-pending discoveries that are associated with the pattern-recognition algorithms.

This is a dendogram that shows the pulse-field gel electrophoresis profile of various species and serotypes of Salmonella. As you can see, they are pretty similar in nature. If you look at the color spectrum, I am going to show you the mass spec principle component now--I hope you

can see this. Is that legible? Using the mass spec, one can then discriminate those various strains and, by principle-component analysis, they were able to separate these strains and they are able to separate two of the strains that were not able to be separated by pulse-field gel electrophoresis.

This slide shows a raw spectrum of a Vibrio that was associated with a Gulf outbreak in 1998. We collaborated with our colleagues from the ORA and we published a paper on distinguishing various species of Vibrio. This is what the raw data looks like. I don't pretend to understand much of this, but I can at least tell you what my colleagues told me.

By applying their pattern-recognition tools with a single positively charged ion, with the same biomarkers, they are able to smooth out the spectrum and make better evaluations regarding the validity and usefulness of each of the specific biomarkers that are associated with this strain.

Once again, they were able to determine

that not only by using the +1 charge transformation but by doubly charged and triply charged that those charged ions enhance the ability to discriminate the protein spectra which allows them to have much more confidence in the evaluation and interpretation.

So, at the present time, this is what this slide indicates are preliminary comparisons between the two types of analytical tools, the pyrolysis mass spec and the MALDI Tof mass spec. Right now, it seems to be cheaper to do MALDI. The capital investment is much lower here than it is in the MALDI. The cost per analysis is better with the MALDI Tof. However, the taxonomic power, the stability of the spectra and the database, the practicality and use for chemical agents seems to be tilting towards the pyrolysis mass spec.

So, in summary, what I have tried to do is give you an update of what is happening at the NCTR regarding renovation of the facility into a BSL-3 laboratory. I have provided you with some information regarding our DNA-based tools that we

are developing to assess counter-terrorism agents and our proteomic tools.

I have to acknowledge my colleagues who helped me put this together. John Wilkes was the mass spectroscopist and Carl Cerniglia is the microbiologist.

I will take questions.

DR. DOYLE: Do we have any specific questions for Dr. Casciano? Have a seat, Dan. We are going to have some questions for you. Dr. McClellan, in his introductory comments, gave us four questions that he would like the Board to respond to relative to the Food Security Program of the agency. First of all, is the approach the FDA is taking for food security balanced and appropriate? Secondly, are there any gaps and, if so, what are they? Thirdly, is the agency devoting adequate resources to appropriate areas of food security? Fourth, are the time tables that we have seen reasonable?

So, with those four questions in mind, I would like to see what each of you think. Perhaps,

I could start out with a few of my own questions. With regard to the CFSAN extramural research program, which seems to me that there are an awful lot of critical needs that have been identified that the agency, itself, cannot address completely with the resources that it has internally.

One good example; I know the National Center for Food Safety and Technology in Illinois is doing a lot of work to strengthen the prevention and preparedness program. But there seems to be a lot more that needs to be done than can be done by just this one facility.

So I guess I see this as kind of a major gap where there needs to be more extramural funding by CFSAN specifically in this critical area; that is the area of preparedness and prevention. I know my experience has been that a lot of money comes to NIH for food-security research that is in the food-safety arena but much of that, if not all of it, is dedicated more towards basic research and medical issues, clinical issues, and not specifically toward some of the practical issues of food

processing and what can we do to control or eliminate intentional contaminates.

Dr. Thomas?

DR. THOMAS: Let me ask--maybe it was mentioned during the course of yesterday and, perhaps, today, but there didn't seem to be a lot of emphasis on neurotoxins in terms of method development and some of the marine toxins. Are the marine-toxin detection methods being developed at Dolphin Island, for example? Where is this piece of the puzzle fit in?

DR. DOYLE: Dr. Buchanan?

DR. BUCHANAN: I can help you with some of this. We have two laboratories on marine toxins. One of the laboratories is the Dolphin Island laboratory and that is devoted to basically two research areas. One is Vibrio species and that accounts for about 50 percent of their activity. The other is marine toxins.

We also have a second group at our Mercourt Campus that is a marine-toxin group headed up by Sherwood Hall. They primarily focus on some

of the select agent marine toxins, saxitoxin, tetrodotoxin. So it is an active component of what we are doing.

A lot of it is oriented towards detection in the environment, to a lesser degree on how we would get rid of it out of those products. But it primarily detection oriented.

DR. THOMAS: Have you been able to leverage off of, say, for example, DOD or even EPA with respect to, say, the organophosphates?

DR. BUCHANAN: In terms of the organophosphates?

DR. THOMAS: Yes.

DR. BUCHANAN: To a degree. Most of our activities in this has been focused, again, on the detection technologies and how to get them out of a food. It is pretty easy when you are dealing with water. It is a lot tougher when you are dealing with a complex matrix. Actually, that research has been quite successful and so we are really quite pleased with the way that is going.

DR. DOYLE: Dr. Casciano?

DR. CASCIANO: There has been some work at the NCTR in collaboration with Jan with demoic acid efforts, too. So the toxic endpoints are available. We have directed our activity towards the biological efforts but we have small-molecule chemists that are expert in these specific areas there too.

DR. BUCHANAN: The other thing, John, that you need to consider, when you say neurotoxins, that is a really large group. So that includes all of our work in Clostridium botulinum which is a neurotoxin. It includes our original threat evaluation of nerve gasses, et cetera, which the key there was finding out what their characteristics are in food. They tend to be so reactive that they are not nearly as much of a concern unless you got into some pretty strange scenarios.

So we do look at a whole variety of them. So that is a really broad-based question you asked.

DR. DOYLE: All right. We will go with Dr. Nerem. We have got a lot of questions now.

Dr. Riviere, Dr. Pickett and Dr. Laurencin.

DR. NEREM: In spite of the excellent presentations, I still came away with absolutely no idea--maybe I just missed it--as to the size of the effort, what number of people, research staff, involved in Illinois, the number of research staff involved in what Dan talked about. So can I get a little help on that?

DR. CASCIANO: At the NCTR, we have approximately eight people directly working on counter-terrorism efforts and about 15 to 17 that are working on the Food Safety Initiative efforts. So there is some overlap between the two studies.

DR. BUCHANAN: In terms of our program, working with a rough estimate of 200 research scientists, we approximately have, when you look at dual-use projects that are food security and food safety, we account for about 40 percent of our program is associated with that. So you are talking probably in the range of 80 scientists.

DR. NEREM: That includes the people in Illinois?

DR. BUCHANAN: That would include everyone. Now, the one thing that you don't have in that calculation is in Illinois we are also leveraging IIT, some of the industry scientists. So typically what you would have in those activities is take the number of scientists we have out at Illinois which is--Dave can give you a better estimate, but I am going to say there are maybe 20 scientists all together I would say that 60 percent of them are involved in those kinds of activities so we have twelve. Then you double it, at least, for the leveraging that we get from the other groups.

DR. DOYLE: Mr. Levitt?

MR. LEVITT: Just to help further answer the question, I was going to ask Dr. Buchanan to give the size of the extramural funding, also.

DR. BUCHANAN: The extramural funding is $2.83 million currently.

DR. DOYLE: Dr. Riviere?

DR. RIVIERE: I would like to, first of all, get on the record to show an excellent

development of CFSAN research programs in these areas. I was on some previous committees that evaluated this. It was sporadic, spastic, not connected, not integrated with anyone within the agency or other agencies. It looks like a very different program now.

I think the extramural program is always a concern and we are suffering because of $2.83 million. That is a concern and that probably is the answer to the question I have. Every time I have come to these, people are always lacking data on, like, oral pathogenicity. You have come up to risk assessments and you can determine where it is and you can detect it at the other end. But that critical link, really the dose response and the pathogenicity, is just not there.

So now you are dealing with all these exotic agents. There is not good data with the regular food-safety pathogens and that doesn't seem to be addressed in at least what I can see in the research programs coming up. If I had to come with a gap, I would say that is a gap.

DR. BUCHANAN: We would agree. Now, the one thing that we didn't make a presentation on was that we have been trying to work with DOD to find some additional funds there. There is, through their TISWIK program--we are attempting to negotiate some oral feeding studies with Bacillus anthracis. We have, out of our old food-safety program, funded dose-response studies, for example with the University of Georgia on Listeria. Those are just being completed.

But these are extremely expensive studies. They are very hard to get the funds for. They are, particularly if you are using nonhuman primates, politically very sensitive. So that is a real tough area to do research and it is an area that, particularly if you get beyond rodents, it is not one that we would do. We would, in part, turn to NCTR to help in that area or, in this case, with DOD.

DR. DOYLE: Dr. Pickett?

DR. PICKETT: It would seem to me that the mission that you currently have underway is really

pretty significant and the amount of resources that you have talked about applying to the mission seems to be significantly underfunded. So I just would like to, first of all, put that sort of on the record.

One of the things that is unclear to me, and what has caught my eye through all the presentations, is Dr. Levitt's chart on time lines because what is unclear to me, based upon the chart and the risk level, has to do with what criteria is being used to define what is, in fact, low risk or acceptable risk. For example, in terms of in-line detection technologies, what criteria is being applied to decide, in fact, that you will be at low risk?

DR. DOYLE: Dr. Buchanan?

DR. BUCHANAN: In terms of in-line detectors, and please understand that at some point we can't get down to--I would love to be able to give you numbers in some cases. Low risk for us would be to have, for the priority foods and agents that we have developed as a result of our

vulnerability assessment, to have--a green would be that we would have a sensor that could detect all of them in most, 90 percent, of the industries where such technologies were applicable. There is a big technology transfer component into that one.

The orange would be--at the other end of the extreme is that we have some viable candidates that looks like we might actually get to technology-transfer points. The red is basically--it is a nice idea. We don't have any direct applications on the horizon. So we are moving there.

DR. PICKETT: I thought that is how you would quantify it. So my question would be have you mapped, as an organization, the resources that you would need to actually get to these various stages?

DR. BUCHANAN: We have attempted to. It is a very large number.

DR. PICKETT: What is the delta between your current staff and where you feel you need to be as an organization?

DR. BUCHANAN: I will let Joe answer that one.

MR. LEVITT: It is obviously an excellent on-point question. As you know, the government, as a whole, funding in all agencies is a difficult issue. We have budget processes to address them. I think everybody looks at counter-terrorism, whether it is very specifically like in food or very globally like any of the various commissions that come out, show there are very substantial gaps.

So you have both a question of size of the gap and time to get there and how you phase it in. But we are working within the administration to identify not only what the size of those gaps are but what is the most efficient way to phase those in that get the most benefit the most quickly.

The kinds of things that you are hearing today, the need for the laboratories, the need for the research agenda, the need to be sure there is a connection between the science and the inspections, this is what is coming to the top of the agenda

that we are defining.

DR. NEREM: Can I just ask quickly, Joe, I didn't feel like you really answered the question.

MR. LEVITT: The rules of engagement don't let me.

DR. DOYLE: I guess that is far as we go with that one. Dr. Laurencin?

DR. LAURENCIN: My concerns in looking at these different criteria, balances, gaps, resources and time tables is that, again it doesn't appear that there is defined road map to success. Again, just talking about going with Dr. Pickett's comments, I saw 2003, I saw 2007. I didn't see 2004, 5 and 5 to get there. I would think that that would be a part of any sort of presentation in terms of where you are and where you going, so milestones, goals, et cetera, and how to achieve them.

Second, again, in terms of the issue about funding, I sit on an advisory board for NIAMS, the NIH Musculoskeletal Advisory Board. We talk about issues that come up in terms of if you have

funding, what would the funding be. They can define what their funding needs are. Their response is that we can't achieve this funding because all the money is going for security and bioterrorism and all the money goes for that, so there is no way we will get there.

But, if we were working in bioterrorism, man, there would be no problem. We should be able to get our funding. So I would ask you to sort of think about what the needs are sort of define what those needs are because if you are not defining those needs to us, I am sure that it may be more difficult to be able to gain the finding that is needed. The rest of the scientific community I guess is actually feeling the pinch, at least they think that they are feeling the pinch, because funding is actually being more diverted to issues of security and bioterrorism rather than these other primary areas that have been in the past.

In terms of the intramural and extramural affairs, I also have questions about where that is going. A lot of organizations and institutes, they

actually decide what their division of intramural funding and extramural funding is. We had our briefing yesterday where it was discussed that money has come in for this, money has come in for this, we are happy, we are using it.

But a lot of other organizations, they decided where their intramural and extramural funding comes from, what their budget is going to be and what their plan is. Also, I didn't see an evaluation of--I saw the presentation, which was nice in terms of extramural affairs, but I didn't see an evaluation of how successful it is and, in terms of what the goals have been in terms of the different projects. As a jumping-off point for where you should be going with the extramural program in terms of funding.

So in terms of resources, in terms of time tables, these are the questions that I think are needed to be able to gain a focus about what should happen in the future.

DR. DOYLE: Very good. Thank you.

DR. LAURENCIN: Is there any response to

that at all?

MR. LEVITT: I think they are all valid issues. They give you a little sense of funding history. The FDA received, in the supplemental appropriation following 9-11, an appropriation of $153 million. The agency at the time, overall, would have been about $1.5, $1.6 billion. So that would be about an 8- to 10-percent increase.

Out of that $153 million, 97 went to food. Of that 97, 90 went to the field with the primary focus being at the border and in the labs focused on the border. That was viewed as a first big gaping hole. As I described, a lot of progress has been made there. That left only $7 million out of that 97 to be devoted to scientific support that my center provides.

What we have seen, what we have clearly realized, is the picture needs to be much more balanced. That is what we are trying to achieve. That is kind of Point 1.

Therefore, second, most of the gains we have achieved to date that have been described have

been achieved out of redirection of existing resources. We are very proud we have been able to do that, but you can only get so far in doing that. What we are trying to articulate, and we welcome any help you can provide us or point us or things we can improve on, is how to articulate the need. What are the things that we feel, and maybe we are too close to it, hamstrung by is so much of what is driving our need is what is contained is classified documents.

So, once you get past that, it becomes a much more generalized presentation such as you have seen today. A disadvantage of our private discussions within the government is they are private but they do allow us to go into that information in much more detail. So we are pursuing that.

Finally, there is never enough money to go around. It doesn't matter who you are; there will be nobody who thinks they have more than they need. Over at NIH, while the NIH, I believe, did reach their goal of doubling over whatever four-, five-year period

it was. In the beginning, all those were to go to not bioterrorism because it wasn't viewed as a major issue five years ago, and the last increase that went to Institute for Infectious Diseases was $1.75 billion in a base increase which is the same size as the entire FDA.

But, nevertheless, from an NIH point of view, that is money that would have gone to other things. So I think what we have to do is to continue to identify, as best we can, exactly as you say, where are the highest-priority needs. What has not yet come through in a visible enough way is what we see are compelling needs specifically dealing with food products and threats from terrorism is this focussed sector and how to get sufficient resources to deal with both basic and applied research needs, the translational work that FDA does.

But this is also, over the long time, early in the game. I think it will be making progress. The fact that OMB did allocate the $5 million over the summer, that is a signal that at

least they are starting to hear that message. We will continue to push vigorously and we appreciate, certainly, the comments today that a number of you seem to feel that that is a not only viable but an important goal to try and achieve.

DR. DOYLE: Dr. Swanson.

DR. SWANSON: I think that funding or lack thereof is a reoccurring theme that exists here, anywhere, in the community these days. But I do think, with regard to whether or not the program is balanced, combining the ORM approach with the CARVER model I think was a major step forward in making sure that the limited resources that you had are directed in those activities that are going to have the biggest benefit.

When it was just ORM, it wasn't quite targeted appropriately. So I do think that that was a step forward.

One of the things, another reoccurring theme that exists with foods, is always that sample matrix problem that exists when you are trying to discuss in-line sampling, trying to get that hazard

out of the food in some way. I am just wondering if there has been any effort to look at not necessarily the hazard of concern but the different types of food matrices that you deal with in a holistic approach and say, what is it about a high-fat food, or a liquid food, or a very proteinaceous food, that you can identify some common themes so that when an event occurs, or a food is implicated, there are certain protocols or strategies that could be applied that would help get the food out, or the hazard out.

DR. BUCHANAN: That is exactly the approach that we are taking. We divide foods up into certain categories, some based on their physical characteristics, some based on their compositional characteristics. We try to direct our program so that we, particularly on the methodology, are really focussing in on that or, in some cases, some simple techniques for bypassing some of those problems.

For example, if you are dealing with a food system that is multiphasic and you are dealing

with a microorganism--you are almost always dealing with a microorganism in the liquid phase. Some of our most successful approaches on taking some existing technologies and making them useful has been simply to centrifuge the sample and separate the two phases and look in the lower one that tends to eliminate some of the interference problems.

So, yes; we are looking at those in terms of categories. I would like to focus a little bit on the biosensors, the in-line sensors. That seems to be an area that really captures people's imagination. They are looking for a magic bullet that they are able to use in that light. We think it is an important area but we can't put all our eggs in that basket.

It absolutely would be irresponsible to take all of our research dollars and devote it to in-line sensors. We can get as much bang for the buck in coming up with being able to pasteurize a product appropriately or look at the packaging technology. So this is really one where we have to look at the specific food, the specific agent we

are concerned about and then look for the specific attributes that we can take advantage of. There really is "no one size fits all" here.

MR. LEVITT: Could I just amplify on that a bit. I think your question really hits an important point which is that, in the products we regulate, we have an enormous breadth and variety. If you just take, say, under whatever assessment, the top ten or fifteen foods out of hundreds and the top twenty or thirty agents, already, ten, twenty foods, twenty, thirty agents, multiply it out. You are talking lots of different combinations.

So, number one, we have to narrow it down somehow and we are. But, number two, we have to look at common themes and not feel like every single one needs to be reinvented. So we are constantly looking at how to get two for, three for, four for, out of any particular research project, how to get cross-cutting themes, common platforms, different things that can be done to try and get more cost effectiveness out of whatever

amount of research dollars and capability we have to put into it.

But that is recognizing that the challenge here is incredibly vast and so we have to keep attention on where can we do the most good the fastest while also keeping some room for long-term goals. And that is kind of the balance between the laboratory methods and the in-line sensors.

DR. DOYLE: Could I just follow up on this in-line sensor question. Part of the issue is time line, could we reduce the time line. Mr. Levitt made an excellent comment about there are so many issues out there, there are so many foods, there are so many agents.

But could you approach this from another perspective and get the private sector more involved because if there is money to be made, you can often entice the private sector to invest its own resources to go this direction. But I think the private sector needs guidance as to what are the areas, the types of foods, the types of agents, that they should be focused on.

I know there are programs with security and all, but that is a thought anyway in terms of reducing the time line and, perhaps, coming up with an effective approach.

Dr. Rosenberg?

DR. ROSENBERG: Actually, my comment expands on what you just stated. I get the sense in the years that I have been watching the funding situation here is that it is clear that the agency that you are within doesn't recognize your agency as a research-based agency. They give you money to protect our borders. They don't give you money to do much research. They give all the money to do research to NIH. You stated it another way, but that is the reality.

It seems to me you have a couple of choices here. You either have to somehow convince Congress or Homeland Security or whoever it is that hands out money that more of that research dollar should be divided and come to FDA over other agencies that it is given, or something that I don't think you do very well because I don't think

you do it well historically, maybe because, again, of the role you play, somewhat insular and having to protect the nation against everything that is out there.

But, in this case, I am wondering if you are properly leveraging interactions with the industry, meaning, I guess the food industry or the diagnostic and tools industries who will make products. If they can see some advantage of those products being used to do this testing and there is money to be made, they will make anything you want to. They follow green stuff around.

All you have got to do is make sure that those needs are such that they want to work on them. You don't have to develop all these tools yourself, I think, if you can leverage them. I began to hear that today. I think this thing you have done in Chicago sounds pretty interesting. It is the first attempt at that. Maybe you could be doing a lot more and maybe even leveraging not just with industry but maybe even some more leveraging with NIH, itself.

I am wondering if your interactions with NIH are strong enough to try to leverage what they are going to spend in microbial disease and what their endpoints are, whether, again, there aren't ways you can gain from that in that a lot of those detection tools and the tools that they are going spend money on can also solve problems that you are trying to also solve.

DR. DOYLE: Dr. Buchanan.

DR. BUCHANAN: Let me respond in part. I don't want to appear defensive on this one but I would like to go back to our estimation that, in 2007, we would still be in the orange in terms of in-line sensors. This is a good scenario. In-line sensors have been a dream and active research area for foodborne pathogens for about a decade. Would you agree with that, Mike? It is about a decade of use.

When we came up with our estimate of what we would be able to achieve, we had no thought at all that we were going to achieve this all in-house. What we were looking at was that, by

strategic investment on our part, leveraging with the industry, leveraging with the people that are actively doing this type of detection-sensor research, which has been, to a large part, some of our national laboratories, not us.

But it has been out in academia. It has been out with some of the other groups. Under the best-case scenario, and unless someone got really lucky to have a broad array of biosensors and get the problems that we are hearing about from industry solved--at this point, it is primarily a development. So, yes; somebody might be get lucky. But to get these solved and then the technology transferred within a five-year period is a pretty optimistic viewpoint on a technology that has had ten years of problems making the leap from basic science--it works really well in the laboratory--to it works really good in a processing plant or dealing with the wide variety of foods.

I turn to the people that are on the panel and ask do you know other ways of dealing with this that you would come up with a better estimate. We

don't have a lot of money to invest; it is leveraging. We would rely on the fact that industry is interested in the product. Two, there are a bunch of researchers out there that are interested in making that jump. What we haven't seen is that bridge.

There are some really great ideas. We haven't seen the translational research that have taken those great ideas that work really well in air sensors and then making that transition to will it work in the milk stream, will it work in a truckload of produce, will it work well in a stream of ground beef which represents some really tough application areas.

In part, if you people have a better way of estimating how long it is going to take, we are trying to be realistic so that we don't overpromise something too often. In this kind of research, we hear a lot of promises. We don't see a lot of, here is what actually going to happen.

DR. DOYLE: Dr. Thomas?

DR. THOMAS: I have a couple of comments.

First of all, I would like to see some priority setting in those outlying years, 2004, 2005, sort of make a jump there. Certainly some of that is predicate upon what you have accomplished this year so you might not be able to fill in all the blanks, but I think some sort of priority setting might be to your advantage.

The other thing, and it is just a generic observation, your regulatory agency. As soon as you start talking about research, you have got to go head on with the NIH. So I would forget about using the term research. I would talk about methods development because that is really what you are doing.

These methods development are extremely important to your mission. Now, I realize we are maybe arguing semantics but I think you have a better chance of selling your programs if you say, yes; we are in food security but we need the methods development, and just avoid the word "research," that very simplistic approach. But maybe that is naive remark on my part, but,

otherwise, you just get painted with the broad brush of a regulatory agency. "That is not your mission." Well, methods development is your mission.

DR. DOYLE: I think we are getting hungry. So why don't we take a 45-minute break and reconvene at 1 o'clock. I know there are more questions. We have more time at the end of the day to ask more questions. So save your questions and let's reconvene at 1 o'clock.

[Whereupon, at 12:15 p.m., the proceedings were recessed to be resumed at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:10 p.m.]

DR. DOYLE: This brings us to the open public comment part of the program.

Open Public Hearing

DR. DOYLE: Do we have anyone from the public who would like to make a comment? Seeing none, I guess we will move on with our agenda

Do we have any other discussion that we cut off at lunch that we want to continue before we get into the next speaker? We can pick up on the discussion later.

That, then, brings us to Linda Youngman who is the Director of the Office of Research at the Center for Veterinary Medicine. Linda is going to address the issue of Animal Feed Safety System, BSE and food-security research at the Center for Veterinary Medicine.

Dr. Youngman.

Animal Feed Safety System, BSE and Food Security Research at the Center for Veterinary Medicine.

DR. YOUNGMAN: Thank you. I am speaking

on behalf to day of Dr. Stephen Sundloff, our Center Director. I am going to be talking about our Animal Feed Safety System, what we have been doing to protect this country from the possible emergency of BSE and also some of the food-security research we have been conducting at the Office of Research.

Our mission is to conduct research to insure public health, the safety an animal-health products and also the safety of animal feed in this country. I want to show this slide. I always try and get it into my talks if I can because I am so very proud of our scientists with their unique training and our unique facilities.

This is an overhead view of our Nierkirk Road Campus. Some of you visited us about a year ago to see how we prioritize our research programs. This little building here is about three floors of offices and labs. That is where we have our laboratories. We have about 165 acres total, about 70 staff. What is unique about our facility is we have large animal research buildings and surgery

suites with a pneumonic table that you can do horse surgery on.

Specialized laboratories, I have already mentioned. An aquaculture facility that is just there. Pastures, a feed-mixing facility which Bob Buchanan showed you a picture of that. And we also have a quarantine facility just off here. So we have very unique facilities to support large-animal research and also counter-terrorism research.

So CVM has four broad approaches to our counter-terrorism efforts. We first consult with different government agencies and different centers within our own agency. We participate in numerous emergency-response networks. We also spend a lot of time focusing on animal-feed safety programs and research. Finally, we have dedicated research programs on BSE and other matters that are important to the Center for Veterinary Medicine.

Under consultative, CVM veterinarians provided assistance to and consulted with the U.K. Department of Health during their 2001 outbreak and foot-and-mouth disease. Then, some months later,

these same veterinarians attended foot-and-mouth disease training exercises in the U.K. and helped to compile a rather thick document of lessons learned from the U.K. incident so that we have procedures in place. So, if something like that happens in this country, we have thought through and learned from the U.K. experience to try and figure out what we need to do here to solve the problem quicker.

So that was a very important piece of work because if I were a terrorist, this would be a very easy way to attack U.S. agriculture. Foot-and-mouth disease is highly communicable and we want to protect this country from it.

We also consult with CDER on procedures for providing animal drugs for human use should the human drug supply be tampered with. So these are some of the consulting work that we do.

We also participate in the National Response Plan with integrates procedures for how federal agencies should work together to respond during an emergency. We also participate on a

working group, on agents of bioterrorism for the NCCLS group, which stands for National Committee for Clinical Laboratory Standards.

We have recently initiated contact with the Laboratory Research Network which is coordinated by CDC. We also recently became involved with FERN, which you are going to hear about next. We have also participated in COOP, or Continuity of Operations Exercises. We have participated in other exercises as well but we can't name them.

Under animal-feed safety, CVM has developed a system. It is a proactive, preventive system to prevent accidental or deliberate contamination of animal feed. We are working with feed manufacturers in this and I will tell you more about that in a bit.

We also actively conduct animal-feed safety research. These are, right now anyway, surveys of foodborne pathogens to establish baselines. You need the baselines to know what are the naturally occurring levels of foodborne

pathogens in feed. So if there is, perhaps, a subtle outbreak or some contamination, you have a quantitative comparison level.

Under research, I am going to talk about BSE and our development of methods to detect prohibited proteins from prohibited species in animal feed. This is a really very important issue for CVM. This is to help enforce the FDA's feed ban.

We also are doing a lot of surveillance programs. I will mention several of them. One is NARMS which stands for National Antimicrobial Resistance Monitoring System. Again, it is to establish baseline levels of naturally occurring foodborne pathogens in retail foods.

Pulsenet, which is an extension of NARMS, which is DNA fingerprinting of foodborne pathogens, to try and detect are there some that have been genetically altered, for example. Also microbiology source tracking to identify the animal origin of foodborne pathogens. Finally, I will finish off by talking about rapid-test methods,

both microbiological and we want to possibly extend that to possible chemical contaminates in animal feed. These studies represent only a part of CVM's ongoing research.

I want to talk a little bit more about the foot-and-mouth disease. I said that CVM veterinarians went to the U.K. during the outbreak, and they came back. Some of the key lessons learned--you will see a common theme here; assess the human health risks resulting from disposal of the animal carcasses; plan ahead, know what you are doing, be prepared; have systems in place so when something happens, you are ready to go; identify public-health laboratories with adequate biosafety-level standards to test human samples; and conduct training exercises for public-health workers at national, regional and local levels.

Again, these are just some of the key lessons learned but the take-home message here is be prepared. We have a document about that thick that came out of these training exercises. So we know how we are going to respond if something like

that happened in this country.

Now, I want to shift gears to the Animal Feed Safety System. The Animal Feed Safety System is a comprehensive risk-based feed-safety system. It is coordinated by FDA and by state and animal feed-control officials, or AFCO, which stands for Association of American Feed Control Officials.

It involves both complete feed and ingredient producers. The areas of greatest regulatory concern are being identified using risk analysis and working with feed manufacturers who can help us understand better and we can help work with them to identify the greatest hazards and then try to work out ways to mitigate those.

So the Animal Feed Safety System describes how animal feeds should be manufactured and distributed, thereby insuring the safety of the animals consuming the feed and also the safety of people consuming food products from the animals.

So the concept is to develop an umbrella risk-based preventive system, a proactive system, to improve industry's knowledge of how to identify

and minimize problems, particularly those that might be related to bioterrorism.

Just to let you know that I think we are the right track, feed manufacturers supported this approach at a recent, about a month-and-a-half-ago, meeting of people involved in the Animal Feed Safety System.

Under animal-feed safety research, our main objective initially is to establish a network to support nationwide surveys that examine the prevalence and antibiotic-susceptibility profiles of human foodborne pathogens in feed commodities. Later, armed with that information, we want to conduct research and develop intervention strategies.

Why is it important. Again, I keep coming back to this; to establish baseline levels that give you a point of comparisons so if there is a subtle assault on the feed supply, we can pick it up, and it is collaboration between CVM, CDC, NARMS, which I will mention more about later, and the Office of Regulatory Affairs field

laboratories.

In 2002, we did a survey of rendered animal protein products. That work is completed and I will show you a little bit of the data from that 2002 survey in a minute. In 2003, we have been doing a survey of plant protein sources. That work is in progress. In 2004, we plan to survey complete feeds and expand our surveying by involving others in helping us to collect samples.

These are some data from the 2002 survey where Salmonella and E. coli were measured in various feed commodities. Admittedly, the sample number, the total sample number, is quite small. But what you will note, if you just focus on these last two columns, is that the percent positivity in these animal feeds for Salmonella was about 34 percent. For E. coli, it was about 40 percent.

Our plans for the future, again, are to expand our feed surveys utilizing the NARMS infrastructure and ORA district laboratories and offices to help us collect feed nationwide to try and make our surveys more representative of the

nation as a whole. We also want to compare the reliability of new rapid-testing methods to existing cultural microbiological methods in animal feed.

We then want to expand to include tests for suspected chemical contaminates in animal-feed samples. As long as we have collected the samples, let's see if we can get methods up and running for chemicals, also. Also, because we have a feed-mixing facility, which you saw a picture of when Bob Buchanan spoke, we want to investigate the utility of industrial processes in decontamination and pathogen reduction in animal feeds.

Now, I would like to talk about BSE, which is of critical importance for CVM. We want to prevent the accidental or deliberate introduction and spread of BSE in the U.S. To do that, FDA prohibits the feeding of mammalian protein to cattle.

What CVM has done thus far is we have conducted over 25,000 feed-mill inspections to date. Those inspections show right now about a

99.6 percent compliance rate which is pretty darned good. But I will admit to you that this compliance rate is based on inspections of feed-mill records only. The assumption is that if SOPs are in place to ensure feeds remain free from prohibited proteins, then the feed mill is called compliant. But we would like to do a better job than that. We want to measure feed samples. We want to do random sampling with the BSE method.

Just to let you know why this is important, CVM did some estimates about the first year BSE-related costs in this country. These are conservative estimates but we think it might be in the ballpark of about $64 billion because the industry is so much larger in this country than it is in the U.K. because are a much bigger country.

BSE regulation was like $53 million. There is a big difference between the two. There is one thing that I wanted to go back to what Bob Brackett was talking about. I was glad he brought it up. It is not just the monetary cost we are talking about here. There is also an emotional

cost to the public and their perception of the safety of food supplies in this country and also their confidence in their government.

I wanted to say about that, I lived in the U.K. for ten years while BSE was emerging in that country. I know that the public did lose confidence in their government, largely over BSE because the government kept saying, it's not a problem, it's not a problem. And then people started to die. So there is that element of it that we have to be aware of, also.

So how do you prevent BSE? It depends on changing feeding practices, not feeding potentially infected tissues to ruminants. Specifically, the FDA feed ban is a mammal-to-ruminant feeding prohibition. It involves prohibited species and prohibited tissues. The prohibited species are cow, deer, elk, sheep and goat whereas horse and pig are exempt or permitted in animal feed.

It also involves prohibited tissues, meat and bone meal, bovine meat and bone meal, are prohibited but blood meal, milk gelatin and plate

waste are exempt.

Now to talk about our methods. CVM has optimized and validated a PCR-based method for detection of bovine-derived material in complete feed and feed ingredients. We are currently transferring this PCR-based method to FDA's Office of Regulatory Affairs for use as a regulatory method.

CVM's PCR method is viewed by ORA as easier and quicker to perform, the reason being, right now they are using feed microscopy which means you have to examine the feed for hair and bone remnants. That takes a lot of time. So, CVM's PCR method permits more effective enforcement of FDA's feed ban since it permits higher sample throughput.

Here are the details of the method. Again, I said the prohibited species were cow, deer, elk, sheep and goat. Permitted species were horse and pig. We use a universal primer. You can see it has DNA here from both the prohibited species and the permitted ones. By using enzymatic

digestion, in this case here, to separate out the pig, in this case here to separate out horse, we can distinguish between the prohibited and permitted species.

We are currently validating a DNA forensic kit including use of this universal primer. This, again, will greatly increase sample throughput in the number of samples that can be tested by ORA.

The final piece of this, the tissue designation, the only way to distinguish meat and bone meal from blood, gelatin and milk is with antibodies. The gelatin needs to be removed prior to detection. It was shown in the U.K. to increase the incidence of false positives.

So CVM has identified four unique heat-stable proteins that are present only in bovine meat and bone meal. We have developed a novel approach to eliminate this gelatin by using 2D gel electrophoresis based on pH and size. And then we use column separation.

So our next steps are to do an ELISA. We want to produce monoclonal antibodies and

polyclonal antibodies and then establish a capture ELISA so we can distinguish the tissues also.

This is what we are proposing for a regulatory testing scheme. We use the universal primer to determine presence or absence of prohibited species. If it is a negative result, no more testing. But if it is positive, we do a second PCR with enzyme cutting so we can separate out horse and pig. Then, at the end, we use an antibody-based test for prohibited bovine-derived proteins. That is the future that we expect we will be able to do that in the next few months or so. Our expert is here.

I will next shift gears to NARMS which I said stood for the National Antimicrobial Resistance Monitoring System. CVM participates in a number of surveillance systems in NARMS FoodNet and PulseNet. These are all surveillance systems of retain meat and human foodborne illnesses with the aim of, hopefully, using that information to reduce human illness.

It establishes baseline data on pathogens

and provides an alert system should animal feeds or retail foods become threatened.

Here is some data from 2002 where we have been surveilling retail meats; in this case, chicken, ground beef, ground turkey and pork. You can see the numbers that we sampled were pretty large. Some of the states are doing all four pathogens that we are looking at, Campylobacter, Salmonella, E. coli and Enterococcus, and some are only doing Campylobacter and Salmonella. That is why they are bigger numbers, because some of the states are only doing the two.

Most species of E. coli and Enterococci are not generally considered to be human foodborne pathogens because, right away, if you look for the four types of meat that we looked at, the levels of E. coli and Enterococci are pretty high. So, because they are not human foodborne pathogens, however, let's focus on Campylobacter because Campylobacter and Salmonella are the most common causes of human foodborne illness of bacterial etiology.

Right here, you can see a problem with chicken. This is a concern. It is over 50 percent. Even the Salmonella in chicken, and in ground turkey, is higher than we would like it to be. So our surveys are giving us information on these foodborne pathogens and the prevalence in different types of meat. But the next question is what are the antimicrobial susceptibility profiles.

These are data from the Iowa Retail Meat Survey which was the pilot for NARMS. We do have the resistant phenotypes for that study so I am going to show you that. Here we have data for ground turkey, ground beef and chicken breast. Admittedly, the number for this pilot is very small. I also don't have the breakdown of numbers of isolates from the different meats.

But you can see that some of the--in particular, ground turkey, for some of the drugs that we tested, the percent resistance bacteria was fairly high. But this may be based on very small numbers. You have to keep that in mind because the whole thing only has 153 isolates total. But these

are the kinds of surveys we need to do to try and identify where the problems are and how can we intervene.

The isolates, after they pass through for antimicrobial susceptibility testing, go to PulseNet. Pulsenet is the national network for DNA fingerprinting of foodborne pathogens. It is a collaboration between FDA, CDC, USDA, state, regional public-health laboratories. The objective is to reduce the burden of foodborne illnesses and assist during outbreaks leading to faster intervention.

CVM's role in this is to determine prevalence of these four pathogens that I talked about earlier, these four bacteria--sorry--and also, the antibiotic resistance among these pathogens. Then PulseNet's role in this is to develop DNA fingerprintings by doing dendograms to determine genetic relatedness and to submit these to the PulseNet database so comparisons can be made between the fingerprints from the animal isolates, the retail meat isolates, and any human isolates

that are presented to the CDC to see if there is an association between people eating contaminated meat and them getting ill with resistant bacteria.

Next the isolates are passed to our microbial source tracking research team. The ultimate aim of this is to try and identify--again going back to a risk-based system, let's find where our greatest risks are and then try to deal with those first.

So we want to identify the animal source causing the greatest number of human foodborne bacterial illnesses and then intervene to reduce disease. So we want to find out is the biggest problem coming from poultry, pork, cattle? Where is it coming from?

We use various phenotypical methods, genotypic methods. And then we do data mining on all of that information combined to try and see is the biggest problem coming from poultry, pork or where. Then we want to intervene to reduce that risk with that information.

Are we having an effect? This is just

showing you relative rates from 1996 to 2001--I am sorry the data are not more up to date--of laboratory-diagnosed infections per 100,000 people. This is for Campylobacter, Salmonella and Shigella. The good news is what you see is a gentle downward trend for human foodborne illnesses over this time frame.

So, hopefully, CVM's surveillance programs may be helping to reduce that incidence of human foodborne illness. We certainly hope we are having an impact. That is the aim of our survival.

I mentioned that we would be comparing some of the existing culture microbiological methods to rapid-test methods. These are just a few of the microbiological rapid-test methods that we are thinking we will be comparing against.

We also have spent a lot of time developing multi-residue methods for drugs in meat, eggs and fish. Now, these are drug methods for chemicals but we think this strategy is applicable to chemical contaminates. To be able to look at multiresidues in one analytical run, we use a two-phase

extraction and we extract and then measure both aqueous and lipid-soluble chemicals in one analytical run. So we do the water solubles, lipid solubles, combine them, one run.

Here is the data for drugs. You can see here we can detect 18 different veterinary drugs in a single analysis, one run instead of 18. So I know it is not a field rapid-test method but it is a laboratory rapid-test method that, in an emergency, we could possibly use the same kind of strategy for chemical contaminants.

Just to summarize what I have been talking about, we have done a lot of work on foot-and-mouth disease with the U.K. Department of Health. We are also working with CDER to inventory animal drugs for human use in case of emergency. We also participate in numerous counter-terrorism working groups and emergency-response networks.

We have also developed a risk-based proactive animal-feed safety system working with manufacturers to try and identify the greatest risks and then intervene to reduce those risks. We

also have done a lot of surveys to determine baseline prevalence and resistance of pathogens in animal feed and we are planning to expand that utilizing NARMS and ORA district offices.

We are also actively conducting research, particularly in methods to detect and prevent BSE from emerging in this country, developing methods for bovine DNA and prohibited proteins in animal feed for enforcement of the BSE regulation.

We also conduct surveys of retail meats for pathogens, antimicrobial resistance, DNA fingerprinting and to identify the animal origin, the animal species, causing the biggest problem in terms of human foodborne illness. We are also working to develop and evaluate microbiological and possibly chemical rapid tests.

I would like to acknowledge the PIs and the various people who helped me put this talk together. Some of them are sitting here to help answer questions if you have any. I am most appreciative of their help.

If you want more information, this is our

website. And I am happy to answer any questions I can.

DR. DOYLE: Any questions? Dr. Thomas.

DR. THOMAS: Yes, please. The nomenclature for compliance rates with respect to feed or grinding facilities, that is kind of a misleading term.

DR. YOUNGMAN: Yes.

DR. THOMAS: If your whole thrust is safety, this is really a record-keeping activity, isn't it?

DR. YOUNGMAN: At the moment.

DR. THOMAS: You could call it regulatory appliance, because that is probably the law. But if the major thrust of your program is safety, and I realize you need to develop a BSE. You certainly couldn't test for 25,000--well, maybe you could. But it would seem to me that the nomenclature for compliance--

DR. YOUNGMAN: You think we should choose a different word; yes.

DR. THOMAS: I think it is misleading.

That's all. If your main thrust is to protect the public from BSE, if someone reads that the feed company is in compliance, that, to me, would mean, well, it must be free of BSE. But all it means is that they are keeping their records. Is that right? Is that a right interpretation?

DR. YOUNGMAN: That is a good point. We probably should change the term. But that is why I wanted to explain fully what that meant because it does seem--we want to do a better job. We just haven't had the method ready yet.

DR. THOMAS: No; I understand that. But, in the meantime, you could call it record keeping or regulatory compliance because, as it is, it is generic and one could make the assumption that it is safety compliance when, in fact, it is not.

DR. YOUNGMAN: Right.

DR. THOMAS: The other thing is, and this is a question for my edification, do you do any testing for CW? I notice you had elk and deer on one of those for chronic wasting disease or is that the Department of Interior?

DR. YOUNGMAN: We don't do that; no. That seems to be driven differently state by state. It is also a touchy issue in this department.

DR. THOMAS: Okay. I was just curious. Thank you.

MR. LEVITT: Could we just take a minute? Actually, for whatever quirk of history, deer and elk and CWD is the responsibility of the Center for Food Safety and Applied Nutrition, not either the Food Safety Inspection Service which handles poultry instead of the Veterinary Medicine which handles veterinary medicine. A quirk of life, but Dr. Brackett is very up on that. He can give you, I think, a two-minute update on that.

DR. BRACKETT: Two minutes or less, I guess. We have been working with APHIS on the ranch-raised deer and elk. They have an eradication plan that they are putting together and we have worked closely with them in designing their eradication plan such that any of the food products that come from them, or any of the FDA-regulated products--that would be foods, dietary supplements,

or cosmetics, if that were the case--would be addressed by that.

When it comes to hunter-killed or wild animals, that is the domain of the states.

DR. THOMAS: Suppose there is a commercial meat market that coincidentally sells venison. It could theoretically be a mom-and-pop operation, but you don't have any inspection responsibility for that?

DR. BRACKETT: That part would be, if it was the venison. But we normally wouldn't be into a meat market because that would be USDA's jurisdiction. But our guidance or our direction towards that is to lead the commercial industries into producing products in sort of a HACCP-like manner so that one could do a trace-back and show that meat or the ingredients actually came from a CWD-free heard.

DR. THOMAS: Thank you.

DR. DOYLE: Dr. Laurencin.

DR. LAURENCIN: Just a couple of questions. I saw the data where you had looked at

turkey and these other types of poultry and found 80 percent levels of E. coli in terms of present in the samples there. But what percentage were of the real disease-causing E. coli? Are you correlating the ones that were antibiotic-resistant with the ones that were disease causing?

DR. YOUNGMAN: That is some work we are doing right now. That is why I showed you data from a pilot that led to NARMS. So we are doing the same kind of work on those isolates looking at their resistance profiles to a whole panel of drugs.

DR. LAURENCIN: Those that are resistant are the ones that are disease-causing, would be disease-causing?

DR. YOUNGMAN: You are talking about E. coli 0157 and things like that?

DR. LAURENCIN: Right.

DR. YOUNGMAN: Yes; we are going to be looking at that as well. I don't have the answer for that right now.

DR. LAURENCIN: Now, in terms of the feed

inspections that are being done, what percentage of the feeds does this constitute and what percentage are you finding in terms of being positive, in terms of--

DR. YOUNGMAN: I showed data on Salmonella and E. coli. For Salmonella, the feeds that we have looked at so far were 34 percent positive.

DR. LAURENCIN: I am just saying containing bone meal and things like that, in terms of violations, in terms of containing bone meal from cows and things of that sort, the BSE--

DR. YOUNGMAN: We haven't done that kind of an inspection of the feed to look for bone remnants or hair. ORA field laboratories are doing that.

DR. LAURENCIN: Okay.

DR. YOUNGMAN: Hopefully, as soon as we finish development of our method, that is going to be chaired out with the ORA laboratories so that they can run the method that we have been developing.

DR. DOYLE: Dr. Riviere?

DR. RIVIERE: I guess we are here to offer suggestions. That would seem to be more of a priority area because, I mean, again, you look at these and 80 percent of the feed has E. coli in it. Do you follow up on all those samples because I think we have had this discussion in other venues before. Why bother.

DR. YOUNGMAN: If they are not foodborne pathogens.

DR. RIVIERE: Yes; if 80, 90 percent of the feed is going to be positive for E. coli, why monitor E. coli?

DR. YOUNGMAN: The retail meats, you mean?

DR. RIVIERE: Yes, unless you actually follow through on what type of E. coli is it and to start looking at the incidence of a pathogenic E. coli.

DR. YOUNGMAN: But we are following up on that by looking at the resistance profiles on those same isolates.

DR. RIVIERE: So you do that on all the samples that are isolated?

DR. YOUNGMAN: In NARMS; yes. NARMS, if you remember the total numbers for 2002, it was two-and-a-half thousand meats that were surveyed for Campylobacter and Salmonella and about one-and-a-half thousand for E. coli and Enterococci.

DR. RIVIERE: So when you do these samples and you detect E. coli--

DR. YOUNGMAN: At some point, we are going to have to make a choice. I see where you are going with this

DR. RIVIERE: Where I am going is, you know, an 80 percent positive rate, you are not getting any information at all out of it. You are not intervening to reduce that rate, so why put resources into monitoring that if you aren't going to get something out of it.

DR. YOUNGMAN: Obviously, our resources are better placed at looking at Campylobacter and Salmonella which we know are causing the greatest number of human foodborne illnesses which is what we are after, which is what we are trying to effect.

We are going to have to make that choice because we do have limited resources. We all know we have less money this year so we have to make--

DR. RIVIERE: What are your resources on this program? How many people are--

DR. YOUNGMAN: On which program?

DR. RIVIERE: On what you presented today for the biosecurity.

DR. YOUNGMAN: On counter-terrorism?

DR. RIVIERE: On counter-terrorism.

DR. YOUNGMAN: And the Animal Feed Safety System and the BSE development work and our surveys, CVM has about 330 employees total. We are, by far, the smallest center. If I had to hazard a guess for putting together for the BSE work, the surveillance work, the Feed Survey work, my guess would be about--and the people who are working on the Animal Feed Safety System, maybe about 30 total out of 330. Is that about ballpark?

DR. NEREM: 30 scientists or 30 total including support staff.

DR. YOUNGMAN: 30 total FTEs, full-time

equivalents.

DR. RIVIERE: I guess I would echo very similar to what we discussed earlier with CFSAN. This is an obviously major issue and you are going in looking at feed records that you know that if somebody did accidently get bone meal in it, they are not going to market them. So, again, the effort, so, looking at this without really diving into more detail, I know this is tied into other food safety programs--for instance, PulseNet, and all that--to try to find out patterns of resistance.

DR. YOUNGMAN: If I can just clarify. Out of our about 330 people in our center, the vast majority of these people are devoted to review functions.

DR. RIVIERE: I know, but I guess there is a hole here. I would be concerned that BSE--

DR. YOUNGMAN: I guess the next order of business for us is surveillance and compliance and research is kind of way down there on the totem pole. So 30 people actually--I mention we have

about 70 people total at our Office of Research Facility. We have got a large number of them devoted to--

DR. RIVIERE: Oh, I understand. We are here to try to help you. But I guess the point to make a statement of is that that is a very small group looking on a potentially--

DR. YOUNGMAN: Some really important issues.

DR. RIVIERE: --catastrophic issue. Look what happened in Canada with one cow and what that did to a regional beef industry.

DR. YOUNGMAN: And we were involved with that. People in our office in Surveillance and Compliance helped with that cleanup after that incident.

DR. RIVIERE: So I guess I would feel more comfortable seeing the 90 percent E. coli, I realize, is history to E. coli but some of those resources to be implementing your animal-protein detection in feed and going on the premises looking for it.

DR. YOUNGMAN: Although another thing I will say about that is we need to do a survey to know where we are.

DR. RIVIERE: Oh, yes.

DR. YOUNGMAN: 2002 is the first year we really did a large enough survey that we could have some confidence in the results. The Iowa Retail Meat Survey, which was the pilot for that study, only had 153 and you can't really draw conclusions from a study that small.

DR. RIVIERE: Then the question would be then why do the study if you can't draw conclusions from the study.

DR. YOUNGMAN: Well, I think we can draw conclusions from the study. We certainly saw that there was a problem with the Campylobacter in chicken, for example. And Salmonella in turkey and chicken. It points us to where we need to go and it also pointed us to where, okay, maybe we don't need to do so much more work anymore and put our resources in another arena.

DR. RIVIERE: So you are drawing

conclusions.

DR. YOUNGMAN: Right. I knew that was where you were going.

DR. DOYLE: To clarify, you are concerned about both the BSE Research and Compliance Program, or just the Compliance Program?

DR. RIVIERE: I think that the BSE Research Program has come up with what looks like a test that you have validated. So now it is basically translational, if you just get it out to the Compliance Program and focus efforts on that.

DR. DOYLE: Thank you.

Dr. Laurencin?

DR. LAURENCIN: I just want to underscore that, in terms of if you look at cost benefit, in terms of you have given that $52 million versus $52 billion ratio in terms of cost benefit, and so I want to underscore, I think efforts really should be on the BSE end. I know there is a burden of disease that happens with E. coli, but, if you measure the numbers between E. coli, the project involving E. coli versus the project involving BSE

detection, I think it probably pales in comparison in terms of the two.

So I think one of the things I am saying is you have limited resources to go one way or the other, and in terms of national strategy, in terms of this area, I think the issue about BSE is probably a greater and more pressing issue and will have the biggest payoff for you in terms of prevention.

DR. YOUNGMAN: Thank you for your comments.

DR. DOYLE: Thank you very much, Dr. Young.

Next we are going to hear from Carl Sciacchitano who is a Senior Microbiologist in the Division of Field Programs in the Office of Regulatory Affairs. He is going to address what we had heard over and over again, the FERN Program, which is the Food Emergency Response Network.

Food Emergency Response Network (FERN)

MR. SCIACCHITANO: Thank you very much and thank you for inviting me, thank you to the FDA

advisory committee, inviting me to give this presentation on FERN today. I appreciate it.

A couple of things to consider or to put things into context to begin with the FERN presentation. One, this is a joint initiative with USDA, particularly Pat McCaskey's group. Secondly, I want to coin a phrase with Joe Levitt this morning of a national partnership with FERN. It is very important to understand what that really means because, as we go through this talk and you see the types of food laboratories involved in this process, it really is a national effort. I really want to highlight that.

I recognize, during the course of the presentation, the number of different agencies and types of labs that are involved in FERN and the associated complexities with a number of these issues as we move towards protecting the consumer from a terrorist attack on the food supply. So just a couple of things.

The mission of FERN, just to be simplistic here, is to integrate the nation's food-testing

laboratories for detection of threat agents in food at all levels of government. FERN looks at identifying not only biological but the chemical and radiological agents that might harm our food supply.

You saw this theme this morning with Joe Levitt and Bob Brackett and Bob Buchanan; prevention, preparedness, response and recovery. These are the primary objectives of FERN. For prevention, looking at the federal and state surveillance sampling programs to monitor the food supply. This includes domestic and import.

Preparedness; we need to strengthen the federal, state, local capacities and capabilities. When we talk about response, looking at surge capacity to handle a terrorist attack or attacks, or a national emergency involving the food supply. Recovery; we can't forget recovery. It is very important with this initiative to support recall, seizure and disposal of contaminated goods and also, and most important, to provide assurance to the consumer as a whole.

Just a little history before I get into this slide. Prior to 9-11, in the past five years, since about 1998, we have been actively collaborating with federal, state and local partners really to build better bridges in such areas as accreditation, method validation and data sharing. These initiatives have been ongoing and it has really opened the doors for a lot of activities and communication that we really needed approval on before that, all in a goal to enhance consumer protection.

But, as Dr. Brackett mentioned this morning, in February of 2003, Homeland Security Council assembled the Interagency Food Working Group. Really, that was to establish an interagency effort to protect the food supply and minimize food as a target. Three working groups were established; the Interagency Incident and Management Working Group; what Bob talked about this morning, the Vulnerability Shield Working Group; and the Laboratory Working Group which I will discuss.

Out of the Laboratory Working Group and, in conjunction with our past success dealing with the federal and state and local levels, FERN was given specific directives. But, before we got into establishing more of the dynamics and the development of FERN and the logistics that are behind FERN, one would have to realize the number of different types of food-testing laboratories out there. I like this slide because, of all these activities from routine surveillance to outbreak investigation, and I will just go across, method validation, compliance issues, CT surveillance, you have also the training component, and proficiency that goes along with that.

These are the many activities that are cutting across most of these food-testing laboratories. If you look at the types, that include environmental, veterinary diagnostic, agriculture, clinical and the federal laboratories.

That is a large cumbersome feat. It is complicated. So we set up the following components of FERN. I will briefly go over this for you.

One component, and a large component, is the FERN Steering Committee. The other major component is the FERN National Operations Center which includes the FERN support programs. Then we have what is called the regional coordination centers, ideally, and this is the ideal state, five regional coordination centers. I am going to go into each one briefly.

From the federal FERN Steering Committee member standpoint, we have very good representation from not only the federal side but also the state side. Not too long ago, the correct date was September 9th to 11th, we had our first Steering Committee meeting. Letters of invitation were sent to all the federal agencies and we had good response, you can see on the screen, from the Department, from FDA, from ORA, CFSAN, CDC, the various parts of USDA, FSIS, APHIS, AMS and GIPSA.

We had Customs, DOD, FBI, EPA. We had representation from APHL. We had representation from the ag community, public health and veterinary diagnostics, again, going back to what Joe Levitt

said this morning, a national partnership.

Some of the FERN Steering Committee responsibilities include FERN guidelines, policies and procedures. Again, bear with me, this is an overview of how we are going to implement many of the activities under FERN. It is ideal to coordinate, integrate and develop national resources to support FERN. They will have oversight development of the FERN National Operations Center and obviously provide support and guidance to the FERN support programs.

While the management of the FERN lies within the FERN National Operations Center, and to go over some of the issues that this center will have to deal with, are the responsibilities of the day-to-day operations of FERN. A lot of this has been done by collateral duties and we recognize that full-time support needs to be included and we are trying to achieve that.

Oversight and implementation of the policies and procedures; again, I want to mention that a lot of the issues and exercises will lead to

harmonization and standardization of a lot of these processes so people are communicating and collaborating and we are doing the right things the right way.

Looking over--not over, but looking to coordinate regional coordination center activities, looking at what the FERN support programs have to offer and making sure those are implemented in the regional coordination centers. You can see the flow of logistics are coming down to provide that harmonization; communication establishment and looking at, obviously, the needs and capabilities of what we need to do. We have to direct the right resources to the right places.

To do this, initially, we have set up five subcommittees; Training, which is being chaired by Todd Bozevich at our Division of Human Health Resource Development out of the Office of Regulatory Affairs; Proficiency Testing is chaired by Bob Buchanan; we have the Method Development and Validation Subcommittees. That is being chaired by Linda Kelly at USDA. We have a Surveillance

Subcommittee chaired by Pat McCaskey and the Electronic Communication Subcommittee that is chaired by Julie Stocklin out of ORA.

I would be remiss not to mention the hard work and efforts that have already been devoted to this process provided by leadership from CFSAN, from ORA, from other federal agencies like CDC, from our state counterparts as well to help to devise and develop not only these trainings that are listed here on the screen but method development as well. A lot of effort has gone into this to facilitate and expand our capabilities and our capacities.

As far as the regional coordination centers, right now it consists of the FDA and USDA representation, the state agricultural, the state veterinary diagnostic, public health and any other--well, for that matter, EPA. From the regional standpoint, it is open to participation, especially when you are looking at a voluntary basis, to help provide that key representation and those needs of that region as a regional coordination center.

Right now, I have listed the possibility of virtual hubs but right now we are just trying to staff some with collateral duties to these regional coordination centers to get them up and running. Right now, we have two regional coordination center that are being developed. Once we go and show the proof of concept with these regional coordination centers, we will, hopefully--and the goal is five regional coordination centers, when I say "goal."

There are a number of significant responsibilities the regional coordination centers have from going out, as an outreach program to identify the laboratories in their region, looking at the capabilities and needs of those laboratories, looking at what laboratories will have screening capabilities, what laboratories will have confirmatory capabilities, what laboratories will have both. These things have to be done.

Coordinating the response during a terrorist attack on the food supply, looking at their surveillance sampling program, looking at proficiency programs, hat is all going to be run

through those regions and coordinated.

The other component, it is a mature system. I am going to talk about eLEXNET for a couple of slides, but the issue really involves the collection and storage of FERN-related data. As the slide indicates, we must find a way to share and store critical information like surveillance-sample data, proficiency data and, obviously, test data.

To capture this information for FERN, the Electronic Laboratory Exchange Network is the vehicle to do that. I will explain what that means in a minute. Ideally, and this goes back three years, when we first implemented eLEXNET back in 2000, we were very proactive in looking at the needs of the laboratories. As the slide illustrates, we have a lot of silos vertically and horizontally within the federal agencies and the state agencies.

We have our own let's call our databases that maybe communicate within only that database. We need a system that can communicate a lot of

these activities from inspectional activities, the quality-assurance component, down to even outreach like education. Again, I am trying to make this simplistic but there are so many different activities that are going on within the umbrella of national laboratories, one would want to communicate that and not burden the laboratories to have to re-key information every time they have to submit or enter different data.

So we are very proactive. Again, during the implementation, that was one of the mandates that this has to evolve with the needs of the consumer, and consumer are the government users for this system.

Briefly, eLEXNET is an integrated secure system designed for federal, state and local agencies involved in food-safety activities. It is a critical system, a necessary infrastructure to provide an early warning system, identify potentially hazardous foods and possibly identifying or assessing risks and analyzing trends.

Right now, currently, there are 101 laboratories participating eLEXNET representing all 50 states of which 55 states are actively submitting data into eLEXNET.

Just a brief slide on over the 160,000 sample test records that are in the eLEXNET currently. We just released Version 3.2 a couple of months ago. That includes over 3,700 analytes where one can capture and share data information. Also, there are over 16,500 imported products of information in the eLEXNET.

One of the key utilities of eLEXNET is the GIS reporting functions. As you can see here, you can select on particular commodities, detected, nondetected, and determine which regions of the country are affected by that product. You can have the drill-down capabilities where you can go the region, to your state, to your county.

A future module, if you will, that will be added to eLEXNET is called the National Food Laboratory Directory. This will give the user the utility of determining what laboratories are out

there that can do, or analyze, a particular food, what type of methods they are running for that particular food, in a nutshell, what is the capacity and capability of that food laboratory.

Here, looking at a generic list, looking at Salmonella, looking at--you can pick a particular matrix or specimen type, looking at any disease related to that incident and call on laboratories that can identify it. You also have the drill-down capability looking in a state, determining quickly what laboratories can do what. This is going to be very beneficial for FERN activities and we hope to see this released in the next several months.

I mentioned something being proactive. We are also looking forward to working with the National Animal Health Laboratory Network, NAHLN. They are currently developing their own system, much similar to eLEXNET. Really, if you look at the center of this slide, you will see HL7 Data Exchange.

I am not I.T. and I don't pretend to be,

but all I can say to make sense out of this is that we are working towards common data elements so you can share information that is efficient and not burdensome to the laboratories. We don't want to have disparate systems not communicating.

In addition to that, we are building components like I just mentioned, the Food Laboratory Directory, and the future methods repository which we are going to build that maybe these systems can share. One person might not own these, but we can share that information.

Again, looking at broader picture, again, the future, and this is my opinion, the future will look at many different types of networks and the possibility of looking at common data elements like HL7 so we can rapidly share communication, whatever discipline, whatever food type, and looking at sharing system modules like methods repository laboratory directory and any other type of laboratory or common functions that may arise in the future.

In conclusion, I would like to mention

some next steps for FERN; obviously, resource issues to support the capabilities and capacities of FERN. We are currently expanding FERN's capability and capacity. You heard from Joe Levitt this morning, Bob Brackett this morning and Bob Buchanan how we are trying to, with current resources, expand and enhance the infrastructure of these food-testing laboratories.

In addition, we will continue the important initiative of communicating and collaborating with other networks. We will continue to strive to achieve products from the subcommittee activities, developing food-surveillance sampling and proficiency-sampling programs, developing validated biological, chemical and radiological methods for food, developing and prioritizing training plans and obviously keep the training mode and the expansion of eLEXNET on a continuous basis to meet the needs of our food-testing laboratories.

I thank you for your time.

DR. DOYLE: Thank you.

Do you have any questions? Yes, John?

DR. THOMAS: Thank you. What sort of--you certainly have a lot of interface with several agencies, but I am reminded of the first responders and FEMA. Where does that fit into the scheme of your earlier slide. They were conspicuously absent.

MR. SCIACCHITANO: That is a great question. In initial discussions of looking at regions, we did note the FEMA distribution of regions. But we ended up looking at the five FDA regions. We do need, as we work through this process, not only with the Steering Committee but to include those types of individuals. When we are looking at emergency response and those activities. Those will develop as we develop our operating procedures.

DR. THOMAS: If nothing else, they should be in a system to collateral it off to you once some of the issues have been identified at an early stage.

MR. SCIACCHITANO: One further comment.

We are working with Ellen Morrison of Emergency Operations and her group to ensure that continuity and we are on the same page.

DR. THOMAS: The other question I had, if I may, was one of your bullets pertained to training. Did I understand you had about 150 sites, or that is the goal, 150 labs, or what? Or did I get that wrong?

MR. SCIACCHITANO: I didn't mention specifically number of laboratories.

DR. THOMAS: I guess my question was more related to training and quality assurance and how do you know that Lab A on the West Coast is going to have the same capability as Lab B on the East Coast? Who is going to coordinate that?

MR. SCIACCHITANO: Again, that is a great question. What we have done with the Steering Committee is identify these subcommittees. Let's pick Training, for instance; training through prioritization of vulnerability assessments, methods that are ready to go that have been validated, training problems will be put together.

In conjunction with those training programs, you need to perfect your Proficiency Program to establish that competency and credibility of those laboratories. So, again, you are going out and we have to figure out, again, as we go along what the training vehicle is. There are a number of laboratories that need to have specific training, how do you get that outreach and to include joining that almost at the hip with the proficiency program to make sure those samples that are going into those laboratories that receive the training. That is underway.

DR. THOMAS: It would seem to me that you need a template of technologies at a basal level. You start from there and you build on that so that you can get some quality assurance across the--

MR. SCIACCITANO: If you look across from the subcommittee point of view, from the methods development validation, which includes the research component, the training, proficiency to surveillance, sampling and then the data sharing, there is a continuum. There needs to be a liaison

in each of those groups. As a matter of fact, there are some of the same subcommittees that are on other subcommittees to make sure.

DR. DOYLE: Any other questions? Dr. Pickett?

DR. PICKETT: Just a quick question. The National Operations Center is sort of, I guess, the nuts and bolts of all of this together from a project management function. What is the staff size?

MR. SCIACCHITANO: I thought I would get that question. The staff size--how is this for an answer--the staff size is evolving. We are starting out at a figure and merging towards an appropriate number that can support a huge operation like our own.

DR. THOMAS: Are you running for Congress?

DR. PICKETT: How do you get resources?

MR. LEVITT: A lot of what we are at here, in terms of time, is developing the framework and the plans and the blueprints and we are working within the administration in order to get funding

for them. We need to get the administration to back it before we are in a position to go and explain that to Congress and the numbers and so forth.

So this is a necessary first step in terms of understanding what it is that you need, how to put it together, what it takes to do it. Just like the research we talked about this morning, you need to have all that groundwork done before you can go and say, I need so much money, because if you just go and say, send me money, they say, why. Just like the question before, what are the time lines, what do you and what are your milestones, this is a--it was once a project that is now growing into a bona fide program we hope and believe.

Again, we kind of began with, oh my gosh, what if it happens tomorrow and what is available, how do you do it right. You are seeing now Phase 2 or Phase 3 which is how do you do it right. In putting that together, Carl and his colleagues and John Marazelli, one of Carl's supervisors, co-chairs the committee with USDA.

But, when you saw the number of agencies on that screen, it is a success story even at the early skeleton stage to have that many agencies sitting around a table talking about collaboratively funding something like this. Again, those are first steps in terms when you asked the question.

But we recognize that right now it has more framework and plans and goals and directions than it has hard resources associated with it.

DR. DOYLE: Any other comments, questions? Thank you, Carl.

We have a tough question next. Do we want to take a break or do we want to keep moving? Keep moving? All right. That is the consensus.

Next we are going to hear from Dr. Kathy Carbone who is the Associate Director for Research with the Center for Biologics Evaluation and Research. She is going to talk about facilitating biologics product development to address threats to food security.

Facilitating Biologics Product Development

to Address Threats to Food Security

DR. CARBONE: This is a test. I am not Jesse Goodman. He sends his sincere apologies. He has a very bad sprain of his back and was unable to come today. So you have a poor substitute but I will do my best.

The talk will start with a few introductory slides about CBER, about CBER-CT and then we will go into some more detailed information about the research program and its relevance to the mission of the FDA.

CBER's roles and the products that we regulate; our role is to facilitate product development. We have to be ready to assure emergency use and regulatory approval of best possible safety and effectiveness assessment with products that are needed in a hurry. We, therefore, have to facilitate this product availability. We have to, however, also ensure its integrity and perform the related research and regulatory activities that are required to do these things.

Our role in products; we regulate our vaccines through the Office of Vaccines, immunoglobulins, blood and blood products through the Office of Blood and gene, cell and tissue therapies in that office.

In the CT area, we have 133 active applications, 561 amendments to those and recently, through some unmet-needs projects internal funding mechanism, we funded 93 CT unmet needs.

The approaches that we used to speed product availability and licensure for products that are needed for countermeasures are that we have, and always have had, a long tradition of early and frequent consultations between the sponsor, the end user and FDA. We have the availability for emergency use of a product under IND. We have available to us fast-track and accelerated-approval processes. We do priority reviews. We can approve a product using the Animal Rule, which I will discuss briefly and Dr. Murphy has in her talk as well.

We pay careful attention to risk-benefit

and risk-management issues and we provide incentives. So we try and do the best balance in a risk model of speed and safety.

The Animal Rule, just very briefly. It is obvious in certain conditions there are important drugs and biologicals that reduce or prevent serious and life-threatening conditions in the CT arena, counter-terrorism arena. In the cases where human efficacy trials are not feasible--i.e., there is no wild small pox--or ethical--for example, one would not challenge somebody with anthrax for an anthrax vaccine--then animal efficacy data can be used.

The use of animal efficacy data must be scientifically appropriate. It sounds fairly straightforward. However, we still need human clinical data for immunogenicity, pharmacokinetics. Safety must be performed in humans. Civilian use often includes subpoputions for biologics and the approval is subject to postmarketing studies when any needed restrictions are in use.

Limitations; it is important in this rule

to have a valid animal model of disease. That is often lacking. How we predictably bridge the animal data to humans is an area that is somewhat difficult to address and confidence in the product may still be an issue, even in a valid model.

Availability under IND is another technique we can use to get a product out quickly. It allows rapid access to an unlicensed product if there is an emergency need. It has simplification and flexibility. It is obviously very applicable to counter-terrorism and counter-bioterrorism. It goes hand-in-hand with working towards licensure wherever feasible and there is a rapid turnaround and active assistance from the FDA in that process. Recent examples that have taken a lot of time and energy and with some success are smallpox, anthrax and botulism, biologicals used to treat those or prevent those.

In terms of our research, we focus on the critical pathways to development, and I will just use the same analogy as Bob Buchanan with the bridge, try and bridge the basic to the product.

We target unmet needs with regulatory implications to facilitate development of products. It allows us to make regulation more scientific and less defensive. We can benefit multiple sponsors through our activities.

It maintains our staff on the cutting-edge expertise particularly with biotechnologies and the novel technologies that are coming down the pike. I will give you some examples of some vaccine development utilizing these novel technologies in a few slides. And it provides us with the scientific expertise and confidence to foster objectivity.

It reduces the risk of reflexive over or under protectiveness in the regulatory process. If someone doesn't truly understand what they are looking at, when they regulate, the chances are they will either pass inappropriately because they are reflexively under protective or they might conceivably become conservative and simply say no. So understanding the science and keeping up with the science is critical to a science-based regulation.

In terms of mission relevance of our research program, since I took over for Neil Goldman about a year ago, we have instituted some tracking within the center. One of the areas we have instituted is to have the investigators directly link their research projects to applications undergoing review. So more than 100 biological licensing applications and 342 new investigational drug applications are supported by these research programs.

Over 85 principle investigators, 61 percent of their research programs have either counter-bioterrorism components or are relevant to counter-bioterrorism. For example, some investigators have actually moved into areas of counter-bioterrorism, relevance such as the investigator who has developed a high-throughput assay for smallpox vaccine potency measurements. Some people have moved their programs already based in an important area to include counter-bioterrorism such as neurotoxicity, test development for vaccines to include, say, smallpox

vaccine.

We also analyze the types of research at CBER. Because our researchers are also regulators, they spend about 25 to 75 percent of their time actively regulating. We tend to think of our research projects in very regulatorily important divisions. The most important, or most numerous work, we do is in the area of product safety.

Product characterization; about 26 percent of our programs are primarily designated as a product characterization program in which they develop methods and assays, mechanisms of action, biological responses and disease pathogenesis for example.

Product efficacy; the program is about 20 percent designated as primarily product efficacy, developing surrogate measures of efficacy. This can be extremely critical, for example, despite tens of thousands of children who have received experimental rotavirus vaccines including the product that was licensed, no immune surrogate was detected that predicted protection for disease.

Having an immune surrogate takes the numbers of patients required to test in an efficacy system from down to the thousands from the tens of thousands. In order to test a product, you require disease prevention. A vaccine requires, often, tens of thousands of individuals to test. So it is a major streamlining advance in terms of research.

Clinical-trial design, et cetera, is not always bench research in our case and we have a very active statistical and epidemiological group and 7 percent we will call "other."

The CBER research program; obviously, a research program has to be externally validated and productive. Otherwise, it is not a research program. There have been 369 publications reported from these 85 programs in Fiscal Year 2003. An example would be molecular determinants of vaccine virulence published in Journal of Virology, work on endogenous porcine retrovirus in xenotransplantation, an assay method in detection published in Journal of Virology, again the rapid throughput smallpox vaccine potency assay published

in Journal of Infectious Diseases and a method to assess preclinical smallpox vaccine neurotoxicity which is in press in Vaccine.

This helps us with QCing our research program because it is an external validation but it also is a very important part of research that we perform in the FDA in CBER because actually this becomes public information and is useful to everybody for speeding regulation.

We also collaborate with multiple outside institutions. We track collaborations. We have over 100 collaborations with academia and other government agencies, some with industry. Some of these come with leveraging for funds, contracts and grants and some are intellectual and some are for professional development.

The vaccines become very useful in terms of threats of biological terrorist attacks because, as we all anticipate, one of the hallmarks of a biological terrorist attack is an event that targets food distributed over a wide area that could challenge the ability to respond.

Vaccines are effective and important countermeasures for foodborne pathogens in specific bioterrorism and counter-terrorism applications but, as was brought up earlier, it is difficult to predict the utility of a countermeasure specifically for bioterrorism because the risk of it actually occurring is not completely known. However, if you can do double duty, in that the biologic for addressing a counter-terrorism or counter-bioterrorism application is also utilitarian in other settings, medical settings.

In addition, the whole pathway, the whole mechanisms, are important for emerging infectious diseases and accidental outbreaks are the same kinds of issues we need to address with biologics along with deliberate. Widespread continuing threats are difficult. It is not really vaccines versus treatment. It is really both because sometimes it may be difficult to disseminate treatment and vaccines can be used as a preventative.

Traditionally, obviously, and I will go

through this quickly, there are traditional agents that are addressed. There are agents that can be used and there are also unknown agents. This is just a publication by one of our investigators, Dennis Kopeko, in collaboration with multiple organizations addressing the ability of a live Salmonella vector which can be used to actually insert both anthrax and Shigella and other genes to provide multivalent vaccines.

Many people are thinking that a different vaccine for every agent is difficult. However, multivalent vaccines can be of great use. This is in your handout so I will just go through this quickly.

We have, as was mentioned earlier, the issue of gastrointestinal anthrax and the public-health significance. For us, in biologics, a vaccine that would be effective against GI anthrax attack would be valuable. It is obviously a serious illness and has serious medical and economic impact. However, this is one of the areas where basic-science gaps make it difficult for us

to regulate products in that the whole notion of what is gut immunity, how does it work, is really poorly understood.

If we ever regulate a vaccine and want to test it for GI anthrax, a suitable model needs to be developed, whether it is us, whether it is another center, whether it is outside in collaboration, but from the vaccine point of view, CBER would have an interest in dealing with the immune response and the protectiveness through the immune response in the gut.

Botulism toxins is also, obviously, a very important area for us. We have limited medical countermeasures and so vaccines or immunoglobulin therapies are very important and we have done a lot of work with trying to proactively deal with issues of what is a protective response, how do you measure the potency of an immunoglobulin product, et cetera.

Now, I just wanted to point out very quickly for botulism and for cholera that the difficulty of regulating, even in a standard sense,

in these agents is difficult but, when you look at the novel technologies that are being utilized for some of these vaccines, there is no history of regulation. This would have to be created and you need people who understand the science in order to do this.

For example, currently under investigation--these are all public--these are from the literature so these are all public materials. There are recombinant neurotoxins under investigation from yeast. There is, obviously, a good double-duty CT vaccine that uses, actually, an encephalitis recombinant vaccine carrying the neurotoxin, DNA vaccination, inhaled vaccines with a heavy chain of recombinant neurotoxin and even a microsphere encapsulated vaccine with biodegradable polymer. This is really novel technology.

We have within CBER some experts on neurotoxin who are, in addition to doing some work on how to neutralize the toxin, where it goes, where it binds, are also doing important work on assay development as well as the other things I

mentioned earlier.

To expand the box a little bit, there are agents which people don't think of. Obviously, this is not a warfare agent, but this might be an agent of terrorism, children 3 to 35 months can be quite susceptible. This is a very hearty virus, rotavirus, and we have no vaccine. So we have an individual at CBER who is an expert in rotavirus vaccines, and expert in mechanisms.

Recall that the previous vaccine which is licensed was withdrawn by the manufacturer due to a serious but uncommon adverse event of intussusception. The fact is nobody knows why this vaccine seemed to be linked with the intussusception. Nobody knows the mechanism and how do we prevent that with the other vaccines. Knowing more about the mechanisms of virulence of these viruses is, therefore, important.

Cholera vaccine, to just give a quick list of some interesting approaches. Live attenuated but intranasal delivery, oral-killed vaccine, recombinant plant-derived edible toxin, toxin

conjugated to a retrovirus virus-like particle but delivered intranasally, and Vibrio cholera ghosts, essentially the nonliving bacterial envelope. The is devoid of cytoplasmic contents but still looks like the bacteria.

Listeria has been used with DNA vaccination with the hemolysin, oral inoculation with the live attenuated bacteria and, interestingly, the attenuated bacteria has actually been used as a live vaccine vector for HIV. These are all very interesting and novel technologies that we have to deal with.

Finally, to end, trying to be a little "edge of the wedge here," SARS is obviously an important agent. In many cases, it is indistinguishable from an actual counter-terrorism event. It was not, obviously, but there are some similar features. So addressing SARS is like addressing CT. There is some evidence, certainly, in the literature of animals that this can be enterically spread. Coronaviruses can be enterically spread.

There was some interesting reports from Amoy Gardens regarding high levels of diarrhea, recovery of the virus from plumbing and found in the stool of patients as well as animals. So the question is what is the risk of this novel agent in foodborne transmission. We don't really know.

There was a recent interesting report that showed some viral particles in the intestine of SARS patients and they were able to recover virus RNA from the stool and some virus actually from the intestinal biopsies.

So, in summary, facilitating vaccine development is another countermeasure development for foodborne illness. Food security is important to everyone. As you can see, multiple centers here are interested and participate in food security including CBER and, hopefully, the vaccines, anything we develop that could be used for other routes, like anthrax being a classic example, inhalation as well as foodborne.

Prophylaxis vaccination for serious infectious disease; the present of a safe vaccine

and the ability to do some prophylactic prevention with vaccination would be quite helpful. Antisera are important for mainstay treatments for botulism and we currently have--there are interesting humanized forms coming out, human monoclonal antibodies being investigated, and these will all help reduce adverse events and hopefully improve efficacy.

Vaccines, as I have shown you, to protect against novel foodborne infections are utilizing novel technological approaches. Scientific needs include a better understanding of intestinal immunity and protection and oral vaccine delivery, which is, of course, a very rapid, easy and non-expert way of delivering a vaccine.

Finally, thank you very much in advance for your comments, suggestions and for your time and attention.

DR. DOYLE: Thank you for that.

Any comments or questions of Dr. Carbone? Well, I have one. Relative to some of the select agents like Yersinia pestis, I didn't see any

vaccine or treatment identified up there. But there are so many possibilities. If we were to vaccinate everybody against all these select agents, that would probably be impractical. So what is the best approach?

DR. CARBONE: Yersinia pestis, and correct me, Bob, if I am wrong, is not an effective foodborne pathogen because it is rapidly inactivated in food. So that was one of the reasons why it wasn't on this. Obviously, it is very important it CT, but, well, everything is a risk-based analysis. Some of the vaccines will be useful and will be used routinely in, say, the military where there would be a significant risk.

Some could be, particularly if they are stable-type vaccines and particularly if they can be administered, for example, by nonexperts or nonmedical personnel, they could be disseminated and ready to go. In the case of, for example, the Salmonella vector, the ability to give one attenuated bacteria that might carry proteins or genes that produce proteins for multiple organisms

would limit the number.

Every organization has to be considered risk-based and this is the difficulty with CT because you don't really know, necessarily, ahead of time. Now, in the case of many vaccines, if they are properly studied--the smallpox vaccine is effective post-exposure. So if we can do the studies either with the animal models, if we need to, or with a human situation to determine the vaccine works post-exposure, then that would be, obviously, if we had a plan to distribute it appropriately, very effective and not used until it was absolutely needed.

All these things are absolutely under consideration.

DR. DOYLE: Thank you.

Dr. Rosenberg.

DR. ROSENBERG: You had a slide that kind of surprised me. Of all the stuff that is in IND or in NDA effort, 61 percent of those things are now CT-related?

DR. CARBONE: I'm sorry; I talked fast and

I flashed through fast. Those were, of our 85 principle investigators and their programs, approximately 60 percent of those programs, research programs, have a CT component, either applicable to CT or actually addresses CT agents.

DR. ROSENBERG: Okay. Thank you.

DR. DOYLE: Any other comments or questions? Thank you.

DR. CARBONE: Thank you.

DR. DOYLE: Next we are going to hear from Dr. Dianne Murphy who is Director of the Office of Counter-Terrorism and Pediatric Drug Development for CDER. She is going to address medical countermeasures.

Medical Countermeasures

DR. MURPHY: Since I was to be the last speaker, I brought some--as I learned in UVA, if you want people to attend your conference, you have got to feed them. So I brought a little sugar and caffeine to hope that we can get through this part without my looking out and seeing too many people nodding off. Since I think there is an error in

the very last slides about which you really want to hear, you have to stay awake to find out where the error is.

I have taken a different approach to my presentation because, in essence, you are going to hear we haven't really--we have a number of products that are already approved from the medical countermeasures for humans who may acquire these organisms via food and water. Where we have gaps, they are not on the A list and, as you are going to hear, we are still working our way through the A list. So my goal this afternoon was to show you the human medical counterpart of medical countertherapies, what we are doing and how it might be applicable to some of the gaps that remain in food and waterborne diseases.

Our mission statement, basically, is I just stated it, which was to identify gaps in the current medical countermeasures. In other words, we are marching down the agents on the A list. I wish we had gotten to the B list but we are still on the A list, as I said. We are identifying where

we have therapies that are labeled. I am sure that has all been reviewed, the difference between a product that may be used in the practice of medicine versus it having an indication in the label.

We then, after we identify where we have needs, we then say what are the knowledge gaps. And then we try to identify if that knowledge exists. When I say knowledge gap, I mean knowledge gap that we at FDA have. Do we have the data submitted to us? Is it in the agency somewhere because sometimes, and I am sure you are aware of this, companies do studies and they submit them and they may not have made it for that indication or they actually do the study and don't submit the data, but we know that it is around, or it is not done in relationship to development for a product indication but we know from academic or scientific literature that those studies are out there.

So we will attempt to find that information. So what is needed, is what this is saying, to get this product labeled. Who has the

information, if it is, and can we bring it in to the agency? And then we construct an action plan.

Our goal is to assure the availability of safe and effective drugs to treat victims of counter-terrorism and to make sure that people have access to therapies and that FDA is not seen as a pointy-headed bureaucratic who won't allow gentamicin to be used even though it has been around, it has been as old as dirt, I have heard someone tell me, so what is our program here?

Well, we want to know it works so how do we go about making sure that it works for the indication that people are recommending it to be used for?

This is a little background on some of the approvals that have occurred already that are directed mostly for the military--the military uses these--that are directed as countermeasures against various agents both infectious and chemical and radiologic are on here, as you can see. Atropine is used in connection with some of the antidotes to nerve agents as is pralidoxime, diazepam. Then we

have others that have been used for cyanide. This is a skin protectant. This is just a combination, a new way of providing the antidotes against nerve agents so that the soldier or the exposed person doesn't have to do multiple injections. So it is a combination product.

This one is particular important, pyridostigmine bromide. This was the first therapy actually approved under the Animal Efficacy Rule that you have heard mentioned by the last speaker. But these, again, ranging from 1973 to 2002, almost a decade, really were aimed more towards the military type of development program.

Now, what about homeland defense approvals. Potassium iodide, you are all familiar with that, I'm sure. Again, an older product to use to prevent longer-term complications, protect the thyroid gland after one has been exposed to, or there has been exposure to, radiation.

Ciprofloxicin was approved for--this stands for post-exposure prophylaxis. After you have been exposed to anthrax, take your cipro. I

am going to spend a little bit of time today going through that because that was the precursor to the Animal Rule. It is also a good example of how the agency went out and found the missing--I shouldn't say missing; that's wrong. The agency had the various groups get together and bring this in as an application so that we could determine whether this product, ciprofloxicin, would be useful to treat anthrax.

At the time, the need was identified as a product that might treat an organism, anthrax organism, that had been engineered so it was resistant to penicillin or doxycycline. So that is why that was begun. As you can see, we did that in August, 2000. It was approved so we had begun the work well before that.

After 9-11, I am going to go into this process about how the agency basically looks at material it has internally and is able to make a determination, itself, that something is safe and efficacious and actually does all the work, publishes it and tells someone to bring in an

application instead of the usual process where we are waiting for someone to bring us an application and then we review it.

Again, some more. This is particularly important because it makes the product available for children which is another thing. When you are developing products or countermeasures, you have to think about entire populations, now, not just--on the previous side, there are mostly healthy young people. Now, when you are developing products for the homeland security, you really have to have a product to treat infants, children, pregnant women, elderly, people who are immune-compromised. All of those populations need to be considered when you are developing products.

This was important because during--this is sort of like telling tales on yourself, but I might as well, in public, anyway. Right after 9-11, we are trying to develop information for people on how to use various products but, actually, we had published information for how to use some of the potassium iodide tablets that were larger, how to

prepare them for children. The instructions said something like, divide in half or a fourth or whatever.

Finally, someone called us up and said, "Did anybody try to do this?" The answer must have been no because, when you tried to do it, the tablet just crumbled. So developing a more reliable preparation that was at least half the dose, of the adult dose, that smaller children could use because you got down to, like, a fourth of the tablet, and that this could be divided if it had to be, so trying to answer some of those questions or activities with which we have been involved.

Prussian blue is an oral agent that you take to eliminate certain radioactive elements to which you have been exposed. It basically helps bind them and remove them. Again, atropine for children. Again, the earlier atropine was a larger quantity. Atropine is one of those 0.0 products you are trying to calculate based on weight. Errors are very common. So it was important to have atropine preparation that also could be used

quickly for children. That was a program that was successfully approved.

Calcium and zinc DPTA, again a finding that the agency did, and I will explain a little bit more about that, for a product that works--this is an I.V. product that helps bind transuranic elements, radioactive elements, upon exposure.

These activities basically were things that have been done by agency, these last four here. By that, I mean I will give you this one right here as a specific example, calcium and zinc DPTA. We knew that we needed more options, therapeutic options, in the realm of radioactive therapies for exposure to radioactive materials. We knew that the Department of Energy, DOE, had contractors who are responsible for going out and providing therapies, calcium and zinc DTPA, Prussian blue to people who were exposed in accidents in the various nuclear-reactor sites.

We were able to work with DOE and Oak Ridge Laboratories which is where most of the contract was based to obtain all of these case

records. It was hundreds. They literally just faxed them to us, so many every day, and then one of our medical officers sat down with all of these hundreds of case records and developed an assessment of the elimination of radiation and developed a metric, as you would for any study, who had baseline, who didn't, who had interim, how was the follow up, what was the response, what were the endpoints.

He did that and then put that back together. Then, working with our Review Division, we were able to determine that this product does work. It will decrease your load of transuranics that you have been exposed to over time. And it is safe to use in a certain--if used as directed.

So these are examples of how we have tried to go out and find the data to help fill in the gaps that exist. These are regulatory mechanisms that we have used and I am going to go in a little bit more detail on a few of them because they are so critical to our ongoing progress and some of the funding mechanisms that we were able to use when we

did receive some money from Congress to move forward in this arena.

The ways that we can expedite drug development, because I, again, bring this up because it is a long process. How can we help facilitate making sure these products become available. One of the things people think of the agency, or at least the drug part, is as a group of scientists who sit there, wait for the company to back their truck up and unload volumes and then we look at them and tell them what they did right and what they did wrong and decree whether they have been able to pass the approval bar or not.

But, really, that is not what happens, particularly for serious and life-threatening diseases, the agency becomes much more involved early on. I mention that because it gets into trial design. It gets into deciding what are the studies that need to be done. That is really what all of this is about.

You particularly see this in the area of oncology. You see this in the area of HIV in which

we actually had some new regulations in that time period about how to develop mandatory early consultation with the agency for serious and life-threatening diseases.

We have worked with the sponsor on deciding what is the study design that is most likely to provide you the information that we are going to need. It may be different than if you came to us and we were at NIH, we had a different research goal. Our research goal is to have evidence sufficient to allow us to label the product.

And we will work with them in deciding, yes, we agree, these are what the endpoints should be, whether you can use animal models or not. We will also work with them in fast-tracking certain products if we don't have options, it is serious and life-threatening diseases. By that, the agency has said, we are going to be more flexible and we will allow you to submit what we call a rolling NDA. In other words, as you get the information, submit it, not just get it, keep it all and submit

it in one big package, and we will work with you as we get the information.

Accelerated approval was really how ciprofloxicin was approved. The Animal Rule, as I told you, was pirydo. I am going to walk through those because I think they are interesting in how you gather scientific information in not the usual way and what happened here.

This ended up being approved under Subpart H which allows us to approve a product for serious and life-threatening disease if we have a validated surrogate marker, a marker that we feel we have characterized well enough. The surrogate marker here was this concentration of antibiotic over the minimal inhibitory concentration was greater than ten times that which would kill the bug.

This was our marker. Basically, what we did is we said we are going to agree that if you achieve this level in humans and we can link it to what happened in the animals, because you cannot conduct these studies in humans--this is pre-Animal Rule--that we will accept this as a surrogate

marker that the humans are going to behave the same way as the animals did.

In microbiology, we can do this. We have lots and lots of experience in trying to--in in vitro data that others may not have, like for nerve agents. So this is an approach we can use.

We did, however, depend on heavily what has been called Dr. Friedlander's work, his animal model where he exposed monkeys to inhaled anthrax spores. You will see the various antibiotics that he exposed them to. So we went out to DOD and said, we know you have got these studies. We know that you looked at ciprofloxicin and we would really like you to get together with the company that makes this product and see if we think we have sufficient information to submit an application.

We also knew that there was human pathophysiology from the Sverdlovsk accident. I am sure most of you have heard about that where anthrax was released into the environment in Russia from one of their research facilities. It resulted in a number of deaths. We actually brought the

individuals who had gone over there and done some of the pathology and we brought them in and had them present to us, actually got some of the slides.

So we were able to look at the pathophysiology in humans, compare it to the pathophysiology that we had in the monkeys and put that building block of evidence in place. In addition, we had a huge safety database on ciprofloxicin including children which this is usually contraindicated for children.

So this was the way the agency tried to put together filling that knowledge gap I that I mentioned earlier and trying to get a product available to the public.

This Kaplan-Meier curve--you just wish all companies had curves that look like this. Here is your control monkeys and they die if you don't give them anything. Here is your product. Actually, one of these deaths was an accident. They had to gavage the medication and they gavaged it into the lungs.

But I wanted to point out that not only did we have that curve for ciprofloxicin, we also had it for vaccines, penicillin and doxycycline and doxy-plus-vaccine. That is what allowed us to do our Federal Register finding. The Federal Register finding, basically, was, as I said earlier, where we looked at the data we had internally on these products for blood levels and other safety information, plus we sought updates on all of these products on their safety profiles.

We were able to, then, determine, using the data that Friedlander data again, we were able to determine that we thought that these products were safe and efficacious for use in post-exposure prophylaxis if you were exposed to anthrax spores.

We published this in the Federal Register along with a guidance on how to submit it, along with the draft labeling and just said, "Here it is. Somebody submit an application who thinks they can manufacture this." You will have to pass all of our criteria for that, manufacturing, but this is really--the agency did the work.

We did the same thing with Prussian blue but we actually did this mostly from scientific literature that we were able to combine with other information that we had. And, as I already explained to you, the calcium and zinc DTPA. Again, these are Federal Register notices of finding, the agency is finding, safety and efficacy.

The Animal Rule, which was mentioned to you earlier, is to be applied when you can't ethically or practically, because the disease doesn't occur anymore. This is what is happening now with certain diseases, certainly in this country, on the A list; plague, hemorrhagic fevers, smallpox, how were we going to get information for these products.

As was stated, these are the fundamental elements that you must have--if you are going to say a product is approved under the Animal Rule, you have to understand the drug's mechanisms as much as we do in our current state of knowledge. I say that because ten years from now, we are going

to understand more, certainly in the area of antivirals, than we do right now.

You have to be able to extrapolate from the animal models to the response--you should be able to extrapolate from the animals to humans. I am not going to really go over this in much more detail except clearly you have to be able to come up with a dose. You have to be able to figure out from the animals the dose in humans.

That is important because of some of the issues we are running into now because animals may have different species sensibilities or toxicities that humans don't have. So, sometimes, you have to give a higher dose in the animal and you are not going to be able to give that in humans, or, other times, the animal is very sensitive. So there are issues here but it is not as simple as everyone thinks it might be. And then you still have to have the safety assessment in humans.

The pirydostigmine was important because not only was it the first time that we used the Animal Rule but it is an example, again, where we

had a large safety database because it already was approved for another reason. That is one of the problems we are beginning to run into as you get into newer molecules, is you are not having this large safety database. I just brought that up because that is an issue we are going to have to deal with in the future.

The other is that the efficacy part of this--this is very interesting because this is an old system. This is an acetylcholinesterase system that we are dealing with here. We were seeing different responses to the protective effect of the pirydo in different animal species. That would theoretically say, well, you can't use the Animal Rule because why are animals behaving differently. How do you know how humans are going to behave?

You had to work out why the animals were behaving differently. It turns out that they have carboxylase systems or scavenger systems that the lower animals, rodents, that the high animals don't have, higher species, and that actually they had experiments in which, if you block that system, you

can get the lower animals or the rodents to behave more like the higher-level animals. By that, I mean, they then would be protected by the pirydo.

You could give the enzyme to the higher species, meaning the nonhuman primates, and get them to--if you gave them an I.V. infusion, you could then eliminate the protective effect of the pirydo. So, by doing these experiments, you were able to see why, and understand the pathophysiology and explain the differences and then, knowing the human system, you were able to predict what the protective effect would be in humans.

So I thought it was just a very interesting case where you have a new rule. The first time you go to apply it and you have got all these complications, already when you thought you passed one of the big barriers of having the safety database there. So it is very interesting.

So that is what the agency has been to do on its own, working with sponsors, working with DOD, working with DOE, working with a variety--CDC. Actually, you are going to hear a little bit more

about the CDC coming up in some of these activities that we have proceeded with under funding mechanisms using grants, contracts or interagency agreements and, hopefully, some day, there will be bioshield out there so that we will have additional ways that people can move products forward.

One of the things that I mentioned earlier is that, when you have a countermeasure for Homeland Security, you have to be able to apply it to everybody in the population. So we were very interested after the anthrax events--we would get calls; what do you do with pregnant women? What do you do with lactating women? What do you do with children? These products--cipro was counterindicated. We had enough studies where we were able to say that the risk-benefit--you can use it.

There are concerns with doxycycline, as you all know, with teeth staining and bone growth in neonates and stuff like that. So what could we do about gathering additional information? What we have been able to put together is a program through

the Office of Women's Health where they have contracted out for programs, various programs, to look at the pharmacokinetics, the safety profile of these various drugs.

Amoxicillin; you say, why amoxicillin? Amoxicillin, actually, in a pregnant woman, you all know that the volume and distribution is different but they really don't have the PK. So, if you are in a serious and life-threatening situation, you, sure as heck, want to know that you are giving that pregnant woman the right dose and that you are not underdosing her or overdosing her.

So this is an area in which we are trying to obtain additional information. The same thing for ciprofloxicin, doxy, particularly looking at lactating women and elderly. These products, again, doing pharmacokinetics in pregnant women and fetal safety outcome of infants who were exposed for whatever reason to these products. Those data, we are collecting both the pharmacokinetics study data and the exposure data over time.

Additional activities have been working

with NIH's Allergy and Infectious Disease Institute and the Army's Research Institute in our plague studies in non-human primates because the agency actually prior to 9-11 had already begun to look at what data there might be available for gentamicin and other products that have been recommended by various expert groups for use against pneumonic plague and actually talked to the people at Hopkins where the biodefense group recommended this and talked to various leaders in research throughout the country.

The CDC helped us by helping us collect all of the human clinical trials in the Southwest area because it does still occur, as you know. Plague still occurs in this country. So we collected all the cases from the Southwest part of the United States and looked at them. They were all confounded, multiple drugs. It wasn't a trial. We could not come to any conclusion.

So we have been in the situation of trying to define how we are going to get some products approved for the treatment of pneumonic plague.

The way we are going to have to about that is working with NIAID and the non-human-primate animal model which we have already begun--we have already completed the natural-history study with the USAMRAAD and NIAID. We are already looking at our dosing studies and have begun to do the preliminary hypothesis testing of exposure of these animals to pneumonic plague and treatment with different doses before we go into the randomization.

The irony of all this now is that the facilities to do this research and the animals have become very difficult. They have become source-limiting in trying to do these trials. But, again, it is collaboration, as you have heard all day, with many different groups in trying to get this done.

Another thing that we are doing is looking--when you have lived through this anthrax use of antibiotics for 60 days, people have really tremendous difficulty tolerating it. If you have read the CDC reports on this, they stopped taking their medications. Not a good thing when you have

a serious life-threatening disease.

So we have been trying to develop a better understanding of the long-term use of some of these antibiotics and looking at various databases that may have this information. We are also working with NIAID and some academic institutions in developing smaller bridging animal models. We are working in the field with not only plague but viral hemorrhagic fevers trying to see what can be developed in some of these areas.

Now, let me see is this has got the slide with the correction. No; it has still got the error. If you look at this, you will see that Salmonella, something happened. You should not have penicillin there, if you would please correct that. This chloro should be back up on this line here so that it should read, cipro, chloro, the furoxone, and ampicillin for the Salmonella. And then, because you took the chloro off of here, because it was supposed to be up here. It is not approved for Listeria.

So I spent all this time talking about

what we are doing to try to develop products on the A list of agents and, when you get to the pathogens that would be involved in food and waterborne types of activities, you will see that we really actually have quite a few options even though one of these products is no longer marketed.

We still have a number of options, except for when you get to Yersinia enterocolitica. These are approved in the label with specific indications. You can go into our labels and find--I have a long list of products that have these organisms listed as you may use them, but for a specific indication of a foodborne disease, these are the ones that we have for right now.

The next, for protozoa. Crypto is approved in children--this is ironic--but not in adults. So, if you are under eleven, you are approved to take this product. Nothing for Cyclospora. Giardia, pretty much the same as for the Cryptosporidium. Metronidazole for Entamoeba and the pyrimethamine for toxoplasmosis.

These are the labeled approved. There are

plenty of approved drugs in the practice of medicine that you will see recommended, but these are the ones that are labeled. For the Vibrios, I always doxy et al. because it is a huge number of the tetracycline class.

I end with these slides just to tell you that right now, as I said in the beginning, we don't have any programs that are under development for the ones that have these zeros in them.

I have run way over time but I was told that that was okay. So I will end with offering to answer any questions.

DR. DOYLE: Any questions for Dr. Murphy? Comments? Dr. Rosenberg?

DR. ROSENBERG: Did anybody come forward?

DR. MURPHY: Come forward for what?

DR. ROSENBERG: You said that you put out this thing for people to come forward and get it approved.

DR. MURPHY: Oh, yes.

DR. ROSENBERG: Is it all done now?

DR. MURPHY: For the Prussian blue, we

have applicants.

DR. ROSENBERG: For the antibiotics?

DR. MURPHY: I can't say too much about the rest of them. I am not allowed to even say. But, for the one that is public that we just approved, yes. For the tetracyclines, for the doxy, we were able to get that relabeled, yes. That did happen.

DR. DOYLE: Any other questions?

DR. MURPHY: Thank you very much.

DR. DOYLE: Thank you, Dr. Murphy.

Questions and Discussions

DR. DOYLE: That then brings us to the question and discussion section for the end of the day. So if you have any questions or comments regarding this afternoon's presentations and, if not, this morning's presentations, we can address them now.

I have one that I didn't get in this morning so let me try this one. Is the agency actually using new technology to enable import inspection?

MR. LEVITT: Tell me a little more. Are you thinking laboratory things? Are you thinking computerized things? What do you mean when you say new technology?

DR. DOYLE: Across the board in terms of out-of-the-box techniques to inspect imported foods. We are not able to test but a small percentage of imports. We are going to have to be creative in how we go about that. So are we using new technologies that are coming forward to inspect and, if not, are we doing research in this area to develop those new technologies?

MR. LEVITT: I am not at the front line at the border, but I will give you my impression. If anybody from ORA has more specifics, you are welcome to. The agency, among our many large tasks, is developing and expanding on what I refer to briefly as the Import Strategic Plan. The first step in that plan was to have a greater presence at the border. We described that.

The second phase of that is to take the new prior notice and use it better for targeting.

That is only two in a much broader scope of trying to get both more efficient at the border but also a much broader look from origin to final use, more understanding what happens in final--a lot more what happens in foreign countries before it gets here, again, for targeting purposes.

Probably--I am not sure it is what you meant by technologies--utilizing computer targeting systems is one of the things that is at the top of the priority-needs area, of what is really going to help us here, both the ability to get the information in and then have the right computerized targeting to get there.

I think your question had a little more to do with at the border. It is kind of like the border version of the in-line sensor. I don't think we are that advanced yet but I will see if Dr. Buchanan knows more about that.

DR. BUCHANAN: Probably the best example of where we have changed some of or border inspections is the inspection of foods coming across the border for radionuclide contamination.

We have gone to a lot of the area of radiation sensors. We have a greater percentage of the product that goes through that detection system. It did during our Liberty Shield light up several potential problems; in fact, it identified some material that was coming through. As it turns out, it wasn't terrorism but it was lit up that way, and we found some material that way.

So we are trying to adapt these as we can. We do have a portfolio of rapid methods available if we need to start using them. So we continually upgrade our laboratory.

MR. LEVITT: Excuse me. We have someone from ORA who has a little more detail. So I will let her identify herself and speak.

DR. DOYLE: Thank you.

DR. WEKELL: I am Marleen Wekell. I am not from ORA anymore. I am with CVM. But ORA--and it is too bad there isn't someone here because they do have a lot of things they are doing. It is too bad they can't share that. But they are working more closely with Customs now and Customs has a

database and an electronic system that we are trying to dovetail into.

We also are in the process of developing mobile laboratories, microbiological and chemistry, which could be deployed at the border if we need them, the work together with CFSAN, the Moffitt Center on the rapid methods. We are trying very hard to get rapid methods that could be deployed at the border.

And then we have a surveillance system so we can target. But there is very much work being done by ORA and I am just sorry no one was here to represent them.

DR. DOYLE: The reason I asked the question is because Secretary Thompson, I believe it was, who made the point so strongly that we have concerns about food that is imported. There was a lot of press in this area. I think it would be helpful for the agency to let it be known to the public not that we have just hired more inspectors but what are we doing to prevent contaminated food from coming in because I often get asked questions

from reporters, "Well, just hiring more inspectors; is that going to resolve the problem of intentional contamination of foods?" I don't have the answer. I send them to the FDA, but I don't know if you want to talk to them directly about that.

But, somehow, I think it would be helpful to share with the public, to give them a better feeling that good things are being done to prevent contaminated food from coming into the country because we have spent more money on it. We hear that there are more inspections. But only testing 4 percent of food, to me, does not give me a good sense that we are fully protected.

DR. DOYLE: Anyone else? Dr. Thomas?

DR. THOMAS: Just one quick remark. That would suggest to me that you need a post-employment surveillance system to put in place when you come back X months from now after these 800 new hires, how many--some bean counter is going to look at some of those things and see what they got for their money.

DR. ALDERSON: We do have metrics on

inspections. You can count on that.

MR. LEVITT: I mean, this is only a partial response. I may have said it so quickly but, just in terms of activity, it doesn't tell you what you got out of the activity. But the additional people, we went from 12,000 what we call physical exams at the border to 80,000. That is a six-fold jump in two years.

Now, that doesn't take the next story of how many things did you find, how much did it help, is it meaningful and so on and so forth, and your point is, I think, exactly on target. We need to do a better job of explaining what that really means in terms the public can understand.

DR. DOYLE: Any other thoughts or comments?

Closing Remarks--Recommendations

DR. DOYLE: I think we are ready to summarize, if that is all right. Don't hold me to this, Board, because if I say something wrong or could be said better, help me with this.

First of all, I think that the Science

Board has witnesses an impressive example of how quickly and effectively the FDA can response to addressing unanticipated public-health threats and issues, that CFSAN and NCTR, NCFST, CVM, ORA, CBER and CDER have responded expediently and, in Dr. McClellan's terms, in developing 21st Century solutions to 21st Century security problems.

Based on our tour yesterday, well, not a tour but our meeting with CFSAN, I think we had a good--not only a good overview but what, in Dr. Ken Shine's words, a "wow" as to what accomplishments have been made in this area in such a short period of time, just some impressive research accomplishments in a short eighteen months.

Importantly, there appears to be a dual-purpose function here in that there is good synergy between food-security and food-safety research. In particular, we want to thank Joe Levitt and Bob Buchanan and the CFSAN team for the impressive overview that we received yesterday of CFSAN's food-security research program.

In terms of gaps, and I do want to have

the input of the Board here because I may not have captured everything and I may have said something wrong. The first gap I have noted is that the food-security mission of FDA is underfunded. I see agreement there.

DR. NEREM: By an amount we don't know because we haven't been given any information.

DR. DOYLE: You took the words out of my mouth. I was just about to get to that. It would be helpful to develop a road map to achieve goals for 2004, 2005, 2006. There needs to be some priority setting. It would be beneficial to map the resources needed to accomplish the goals as well as provide budget information.

Secondly, there appears to be a need for expansion of the CFSAN extramural research program to address critical applied issues in food security and safety especially in the areas of preparedness and prevention.

Thirdly, there appears to be a need to place more emphasis on determining the dose response of nontraditional foodborne select agents

in foods.

The fourth gap suggests that there needs to be more emphasis placed on translating methods developed from CVM's research activities to the Center's Compliance Program. This, in particular, has to do with the BSE issue. Did I say that right?

The next point is FDA needs to better articulate its needs for addressing food-safety issues. One suggestion I heard was there is a need to identify the agency's methods-development needs as such rather than describing this as a research need because FDA is, in some circles, not considered to be a research organization. So the point is, rather than saying we need more research on methods, the agency needs to have information on methods development and not include the word "research," as one suggestion.

Do we have any other gaps or comments that you all would want to share?

Then I can move on to my personal one and that is I want to thank all of my colleagues on the

Science Board for their commitment to providing FDA guidance that will strengthen the agency's science program. In particular, I want to thank my colleagues, Bob Nerem and Marty Rosenberg and Harold Davis who, unfortunately, was not able to be with us today, but who will leaving the Board.

I also want to thank Jan Johannessen for his first time out of the box as being the staff coordinator here and doing a super job, and Norris Alderson for his involvement with the Board. Finally, I want to thank and commend Commission McClellan for his superb efforts in communicating to the public the FDA's activities and accomplishments in the protection and advancement of the health of the public.

So with that, does anyone have anything else to say?

DR. NEREM: I just think we all owe you a vote of thanks. This is your last meeting and you thanked everyone else. But you did a great job and I can't imagine how you pulled that report together. So, congratulations.

DR. DOYLE: Thank you for that. Joe, you wanted to comment?

MR. LEVITT: Took the words right out of my mouth. I want to thank you for your role, first as a member of the Science Board and as Chair of the Science Board. We really appreciate the opportunity of all the members to present here today.

Just as it looks like I am just about at the end, we will let the Commissioner know that we are just about closing and if he has any final comments.

DR. McCLELLAN: There is that sense of timing again. I see that, as in everything else Joe does, there has been an extreme amount of efficiency here and you walked through quickly. I had a chance to talk a little bit to Dan and some of the others who have been attending about a number of the comments.

I just want to say a couple of things generally. One is that, in preparing for this meeting, and in general this year, we have tried to

think really hard about how we can use our limited resources as effectively as possible. One of the most important prerequisites for instilling public confidence and building up the agency is confidence about us spending the dollars effectively.

I think that we have redoubled our efforts in this area and will continue to do so. I think your suggestions and guidance here are much appreciated.

I just want to conclude by coming back to something that I talked about with you all last night which is the complexity and challenges in our public-health mission. I want to make sure that we are matching that complexity with equally creative responsiveness and technical capabilities. The discussion that we have had today has been extremely helpful in making sure that happens in the area of food security and counter-terrorism more generally.

We are going to have you back in a few months to talk about some emerging scientific and public-health problems in other areas. In the

meantime, if you are interested, we would definitely like to call on you for other advice and we will look forward to following up on some of the comments that you made here today.

One of the things that I have also tried to do is take advantage of resources where I can find them. You can bet that if you give us some specific suggestions--it is not to discourage them, but if you give us some specific suggestions, we will be back in touch about how we can get you to help us follow up on them, too.

So I want to thank you all very much for your contributions today. I especially want to thank Joe for his leadership in the overall food-security program and for the Center for Food Safety and Applied Nutrition at what I think has been an absolutely critical time in which the center has risen to the challenge.

We were talking earlier this month about how we have already had five press conferences this year with the Secretary and have pointed out that the year is not over yet, so there may well be more

coming. It has been a banner year for the center from the standpoint of new progress on food safety, new regulations, new research programs, from the standpoint of applied-nutrition programs as well as we are taking fundamental new steps to make better health information available to consumers and help address the growing challenge of obesity and other opportunities for improving health around better nutrition.

Joe's leadership has just been tremendous in all that. I have valued him as a colleague, valued the whole team. It is a great team at CFSAN, but it starts with good leadership and Joe has been great for that.

Mike and the rest of you who are rotating off, we are going to miss you. We really appreciate the service. As I said before, we are going to continue to call on you, so thanks to all of you for your work on this meeting today and for your continued support for FDA and its vital public-health mission.

This is perfect timing.

DR. DOYLE: I think it has been a great meeting and thank you one and all. I guess the meeting is adjourned. Have a safe trip back.

[Whereupon, at 3:25 p.m., the meeting was adjourned.]