NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

SCIENCE ADVISORY BOARD

October 19, 2010

Table of Contents

Welcome and Overview - 1
Dr. Cynthia Afshari

Conflict of Interest Statement 4
Dr. Margaret Miller

Overview of NCTR 5
Dr. William Slikker

Update from the NCTR Divisions

Division of Microbiology 22
Division of Biochemical Toxicology 37
Division of Systems Biology 50
Division of Personalized Nutrition and Medicine 67
Division of Genetic and Molecular Toxicology 85

Update on Activities

Office of Scientific Coordination 99
Division of Veterinary Services 120
Women's Health Program 135

Presentation on the Center for Tobacco Products 146

Presentation and Discussion of NCTR Strategic Focus and Future Direction 177
Dr. William Slikker

Center's Representatives Report on Future Regulatory Challenges 207

Discussion on the Need for Research and Potential Collaboration 270

P R O C E E D I N G S

Agenda Item: Welcome and Overview

DR. AFSHARI: My name is Cynthia Afshari and I'm heading up Science Advisory Board here for NCTR. I'd like to welcome all of you to the next two days of our Science Advisory Board Meeting.

I want to thank all of you for your journey here and for your participation. I'm really looking forward the interaction between the NCTR division directors, and Bill Slikker, the esteemed Director of NCTR and our Science Advisory Board, as well as the Center representatives who are here from FDA.

I'd also like to welcome the two members from the FDA Science Board who are also with us today.

Today we will hear about NCTR through full immersion. Our goal over the next two days is to try to understand where we are and see where we need to go for the future.

Our role as a Science Advisory Board is to think about how to best pair the talent and expertise within NCTR to the most critical needs within the FDA.

We're looking to everybody to contribute on what those needs are and where you see opportunities moving forward.

I'd like to start at this end of the table and go around with introductions.

DR. WYDE: My name is Michael Wyde. I'm with the National Toxicology Program at NIEHS.

DR. SACKS: I'm Leonard Sacks. I'm the Acting Director of the Office of Critical Path Programs at FDA.

DR. BURCHIEL: I am Scott Burchiel from the University of New Mexico at Albuquerque. I'm a Professor of Pharmacology and Toxicology.

DR. YAGER: I am Janice Yager from the University of New Mexico at Albuquerque, and I'm on the faculty of the Department of Internal Medicine, Division of Epidemiology and Biostatistics.

DR. HINES: My name is Ron Hines. I'm a Professor of Pediatrics, Pharmacology and Toxicology from the Medical College of Wisconsin, and I'm also a member of the Children's Research Institute in Milwaukee.

DR. DOW-EDWARDS: I'm Diana Dow-Edwards and I'm a Professor of Physiology and Pharmacology at State University of New York, Downstate Medical Center.

DR. BAKER: I'm Dave Baker, a Senior Director at Pfizer in Clinical Research, in charge of computational biology

DR. WATKINS: I'm Paul Watkins, a Professor of Medicine and Toxicology at the University of North Carolina-Chapel Hill and the Director of the Hamner-UNC Institute for Drug Safety Sciences.

DR. MILLER: Good morning, I'm Doctor Margaret Miller, also Peggy Miller, and I am the Designated Federal Official for this advisory committee.

DR. SLIKKER: I'm Bill Slikker, Director of NCTR. I'm very happy that you're all here for this fun day and a half we're going to have. I hope to learn a lot from all of you and to exchange a lot of good information about the future of FDA and NCTR. Thank you.

DR. BROACH: I'm Jim Broach from Princeton University, Associate Chair of the Department of Molecular Biology, Associate Director of the Institute for Integrative Genomics, and a member of the FDA Science Advisory Board.

DR. SPEILBERG: I'm Steve Speilberg, a Pediatric Clinical Pharmacologist, currently head of Pharmacogenomics and Personalized Medicine at Children's Mercy Hospital in Kansas City and the former Dean of Dartmouth Medical School.

DR. ASHLEY: I'm David Ashley. I'm the Director of the Office of Science for the Center for Tobacco Products at FDA.

DR. WILSON: I'm Carolyn Wilson, Associate Director for Research at the Center for Biologics Evaluation and Research.

DR. HANIG: Joe Hanig, Associate Director for Research in the Center for Drugs.

DR. GRAY: I'm Richard Gray from the Office of Science and Engineering Laboratories at Center for Devices and Radiological Health.

MR. MYERS: Mike Myers from the Office of Research of the Center of Veterinary Medicine.

DR. FLYNN: Tom Flynn, I'm a Research Toxicologist with the FDA Center for Food Safety and Applied Nutrition.

DR. FARRAR: Good morning, Jeff Farrar, Office of the Commissioner, Office of Foods. I work for the Deputy of the Commissioner for Foods, Mike Taylor, in White Oak. Thank you for having us here.

Agenda item: Conflict of Interest Statement

DR. MILLER: I have to read a conflict of interest statement for the record, and the following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the evidence of such.

Based on the agenda submitted for today's meeting, all special government employees have been screened for their financial interests related to the topics at hand.

FDA has determined that all financial interests in firms regulated by the Food and Drug Administration present no potential for conflict of interest at this meeting.

In the event that the discussions involve any other products or firms not already on the agenda for which a participant has a financial interest, the participants are aware of the need to be excluded from further participation. Such an action will be noted for the record.

In the interest of fairness, all other guests are asked to address any current or previous financial involvement with any of the firms whose products upon which they wish to comment.

Agenda Item: Overview of NCTR

DR. AFSHARI: We'll begin with an overview from Dr. Slikker.

DR. SLIKKER: Good morning everyone. It's really great to see all of you here and I know it's an important day and half for us to have your input on the future of NCTR and FDA.

I wanted to just point out that NCTR is definitely a unique facility and a unique interest in that it was formed by Executive Order in 1971.

We're coming close to our 40th anniversary here in the next year and we plan to celebrate that next fall. We are looking at ways of combining that with the annual SAB meeting so we can have all of you here to join in the celebration as well.

One of the themes you'll see is the idea of international outreach and globalization. That's one of the themes we're thinking about for our 40th anniversary as well.

The idea is a combination and interaction between academic facilities, government, and industry. This is a theme you'll see repeated throughout our presentations because NCTR has the responsibility of bringing these branches together to tackle important, scientific problems and interest areas.

The point of this slide is to show that we are all part of the Department of Health and Human Services. FDA is one agency within the Department, of the sister organizations of NIH and the CDC, and we're so happy to see representatives from our sister organizations, NIH and CDC as well as Centers within the FDA.

The vision and mission of NCTR has changed, and builds on the idea of global leadership for innovative, scientific solutions by approaching and working with public health, and the idea that we do this by developing research strategies to help solve complex problems.

We also do this by integrating across various groups including those from academia, government, and industry. I think it is very critical to do this in a multidisciplinary way. You're going to see that in a broad breadth of presentations later on today.

The facility is quite large. Many of you are new to NCTR, and some of you who have been to NCTR in the past but in a different capacity,and are new to the Science Advisory Board. NCTR has about 550 acres of property that belongs to the FDA. This is not government-serviced property. This is an FDA owned and operated property. This campus represents about 25 percent of all of the property the FDA owns.

We share this campus, called Jefferson Laboratories, with Office of Regulatory Affairs (ORA). ORA is a very integral part of this campus. They joined us here about ten years ago and they have a building some of you will see later on the tour. In fact, the building with the tower on top is the ORA building.

There is about 1 million square feet of floor space at NCTR and it is dedicated to FDA. We can change and reconstruct this facility to meet FDA’s goals. If we decide FDA needs something done, we can have it done here.

It’s a great opportunity. At the same time, of course, the functioning and maintenance of this facility also comes out of our operating budget. It’s a holistic event.

One thing you can see down here is the number of government employees and the number of contract employees. We do have a lot of on-site contractors here. This is very important at NCTR. This includes individuals who take care of the facilities, individuals who run the pathology group, which is

top notch, and those who take care of the animals and diet preparation, et cetera--all very important people.

There are employees who have been here as long as or longer than I've been here, which is many decades now. These people stay with us and we actually consider them part of the NCTR team, because they definitely are.

We also have a lot of special employment opportunities for post-doctorate fellows. I'll go into this in more detail later, but this is a very integral part of the matrix of NCTR/FDA.

It is so important to have these new individuals come into our facility for training. Some of them may stay. Many of them go out into other parts of FDA, other parts of government facilities, or into industry. This training program is very important to us.

Then, of course, we also have about 30 or so staff from shared services, which are headquarters, as well as the Arkansas Regional Laboratory ORA Facility, which is one of five major ORA facilities across the U.S. They have a little less than 100 individuals there.

You can see the diversity of activities NCTR can maintain. Some of them, like the phototoxicity labs are located here, and there are only two or three of these in the entire world.

We also have primate laboratories that some may get a chance to see later if you'd like.

These are all designated to really aid in FDA's decision-making process. Multiple species are available on this campus. A bioimaging center, which has just been constructed in the last few years, is growing as we speak. There is also our visiting scientist housing that is just down the road. This allows a proper transition opportunity for those who are coming here to work at the NCTR facility to get oriented into the community. It is usually used for visiting scientists, academic, and graduate students. This facility is one that's designed to do the work of the FDA, and it can be modified, changed, and enhanced to do fulfill to FDA's mission.

I just want to give you a few words about our structure. The coordinating council is really the day-to-day management of NCTR. You'll meet some of these people, or already have here on the right hand side. It's very important to understand that we meet on a weekly basis, but we usually have daily interaction. All of this has to do with the planning and resources that Jeanne Anson, our Executive Officer, maintains, or the safety and health side that Jennings Partridge, maintains.

Tom Flammang is in the Office of Research and a close advisor to me and others here, and Paul Howard is a scientific

coordinator. And, of course, many of you already know Peggy Miller.

Doctor Miller is the Associate Director for Regulatory Activities. She is actually in our NCTR office in White Oak. White Oak has a nice location. We're above the large cafeteria looking down on the crowd so we have great access to them. They come by and visit Peggy routinely.

Now, on the left hand side are the Research Divisions. You're going to hear from each one of these individuals today for an update of not only what new things we're doing, but also how they responded to your recommendations from previous reviews and get a real sense of the scientific work that's going on here.

Some of the Division names have been slightly modified. Donna Mendrick, for example, is the Director for the Division of Systems Biology because we're also looking at prevention and efficacy, not just toxicity. That has been broadened in scope.

Also, Martha Moore's division is the Division Genetic and Molecular Toxicology; reproductive toxicology is covered in two new groups and is no longer just in Martha Moore's division.

The NCTR working groups are very important to us because these are areas of overlap, expansion, and emphasis. Nanotechnology, chaired by Paul Howard, is a really important

area in which FDA-wide collaboration, especially from ORA and NCTR, is moving nanotechnology forward.

Imaging is an expanding area for us. We have a group that's leading this area forward, including PET imaging as well as MRI and CT.

Women's health is a very important and expanding area for us too, coordinating tightly with the FDA's Office of Women's Health, but it also involves studies that can be done within that framework.

Then there are two new groups, the Reproductive Toxicology Group, chaired by Deb Hansen, and the Developmental Toxicology Group, chaired by Sherry Ferguson.

These are important areas for us. What we've found with developmental and reproductive toxicology is that it started to be involved in each and every division out here. It really wasn't covered by any particular division.

We had biochemical toxicology that had developmental studies going on, such as VPA. You had studies going on within neural toxicology, such as acrylamide, BPA, and methylphenidate. And then there were studies within the area of Systems Biology.

Deb Hansen is in charge of these cross-cutting working groups, a very capable reproductive toxicologist, and past officer of the Teratology Society. And Sherry Ferguson, who is

well-known in the developmental neural biology area, is in charge of the neural toxicology studies.

These will help us move forward and, in fact, the members of the groups are here. You can also see that we have individuals interested in pharmacokinetics. We have individuals interested in behavioral and functional assessments, as well as those interested in stem cells and other kinds of models for screening capabilities.

Deb Hansen is on both committees to help coordinate those two. We thought this was such an important area that cut across all the different divisions out here so we made them two working groups.

They are treated, in many ways in terms of the review capacity, as the divisions are in that they will receive concept papers from me to review that are in the area of reproductive developmental toxicology and help give me input on those areas.

And now to advancing the science of the FDA: You're going to hear about all these particular areas today and tomorrow. We are a part of the tremendous transformation going on in food safety right now.

Nutrition and obesity, especially within our Division of Personalized Nutrition and Medicine, is also experiencing change. Bioinformatics is very critical. We were just talking with Jim Broach on the way in about generating lots of data but

how do you interpret it? You need good bioinformatics, and we certainly have a very good team here. Weida Tong heads up that group within Systems Biology.

You'll hear a lot about safety assessment. The whole idea of moving forward with safety pharmacology and safety assessment was one of the recommendations from the full FDA Science Board. We have certainly incorporated that into our thinking for the future.

Biomarker development is so critical. Here is where you develop those new approaches that allow you to make better decisions, and we've already talked about nanotechnology. You'll hear more about that and bioimaging.

And then of course, regulatory science and training is a real expansion area. We were so pleased when Doctor Hamburg, Peggy Hamburg, moved the idea of regulatory science forward because we feel like this is the essence of NCTR— the idea that you're taking important science and translating it for usefulness in the regulatory environment, and the developing and training of personnel to work in that area.

Right now we feel like NIH has not been able to train enough people in this area and the pharmaceutical firms, as well as the government, are looking for a pipeline of students who have the ability to do regulatory science.

We feel like we need to fill that gap and we're doing it both by training domestic students as well as international students. We're reaching out to various countries, pulling in their students and training them here, and also exchanging students with them to go to the facilities in those countries around the world. We're very much integrated with the international group within FDA to train individuals in the regulatory sciences. These are some areas you'll hear about throughout the next day and a half.

Let me just finish up by talking about the mechanisms to support cross-agency priorities. This is really important to us because this is where this particular group is so important to us and our representatives from the various centers.

The NCTR Science Board itself is so critical because it is your input that helps drive us into the future as far as where we should be putting our emphasis is concerned.

There's, of course, coordination as you see here. Almost at every one of our annual meetings we've been able to have one or more representatives from the FDA Science Board to ensure coordination and good communication. I'm so happy to have two here on this particular occasion.

The NCTR Strategic Plan— this is not only devised by the researchers at NCTR with input from the Science Advisory Board, but we then take it to the centers to get their input and

then we include that in the final version. That version is only good for one year or less because then the whole system starts over again, and we review and improve the plan each and every year.

We do have a five-year strategic plan looking out to the future. It's one that is very critical for guidance and for the input from all of the FDA into what NCTR does.

Most of us are in the area of FDA proposals. We know about Optimum's Health Critical Path Challenge Grants, and I know all of the people at this side of the table are very competitive for those.

It's an important area that provides exchange because many of those areas emphasize the idea that you work across centers in order to accomplish a goal, and often times reach outside the Agency to get different collaborators to come in and help in those areas.

The product selection committees collaborate to help select compounds that are of high priority, which will be explained further by Paul Howard. Some of those that have been coming up are certainly recognized as such.

One doesn't have to say too much about BPA to realize it's a high priority area. The chemical selection group works within FDA to find more of those compounds and agents that need studying. They do it in a very systematic fashion by having

meetings at least twice a year to bring together scientists from the rest of FDA, and from NIEHS, NTP, and NCTR to select the agents that will be studied.

Then, we review those studies systematically so that we know its proposal is right, the protocol is correct, and that the data is being analyzed correctly for use by the FDA reviewers.

Regulator-initiated research is another mode. One example is pediatric anesthetics, which has been such an important area for FDA during the last several years.

We are now transitioning from fundamental animal studies, which indicated that there may be issues with exposure to anesthetics, almost all anesthetics unfortunately, during certain stages of development. We're talking about late pregnancy up to early years of childhood.

The issue is that at certain doses, at certain periods of duration of anesthesia, there seem to be issues. We're trying to understand how that translates to humans.

This was a study that was initiated between CDER and NCTR, and has now grown to be larger than that to include lots of researchers outside of the FDA. We're bringing in important clinical data to move that study forward.

Finally, the investigator-initiated research: Here we've actually realigned some of our divisions to be more

receptive to this. For example, we've added individuals to the computational models. Jeff Fisher just joined us as a modeler, which is very important to us.

The translational biomarker is also critical. We've added a new center within Systems Biology— Innovative Studies where they're looking at those kinds of approaches. And then, of course, food safety is one on which we have a close handle on as well.

These are areas where the studies come from the researcher at the bench noting that, from their experience and from their exposure, these particular studies need to be done. They're percolated up. The concept paper is checked against what the rest of the centers within the FDA would like to see done. If it meets needs, it is approved by that process to move forward. Those are some of the techniques we use to focus resources across NCTR.

Let me just finish up by talking about this slide which sort of summarizes what I've just been saying— it's the idea that we have input from strategic plans and from the Science Advisory Board to plan and carry out good studies. They are often times done between Centers.

We figure that about 60 percent of our studies have PIs from other Centers within FDA, and many others have representatives or co-PIs from other agencies. That is accounted

for in our experimental plan. Experiments are conducted and the results are communicated.

At that point in time, hopefully they are of direct relevance and use to the FDA regulators. If not, things have to be improved or methods have to be expanded, studies have to be expanded. That can be done based on feedback since we have input along the way from the FDA centers, both at the concept paper stage, which is just a two-page document early on, and at the full protocol stage where it's reviewed once again.

This cycle is so important to us. The communication and the exchange with the other centers of FDA is critical to this, and so is the input, of course, from the Science Advisory Board.

Let me just stop there. I'll be happy to take any questions you may have and then we can move onto the presentations from the individual Divisions. Do we have any questions?

DR. AFSHARI: Bill, I just wanted to ask you if you said 6 percent of the Center budget?

DR. SLIKKER: 60.

DR. AFSHARI: 60. Okay. I was thinking it sounded low.

DR. SLIKKER: No, 60 percent. It may be higher than that but it's at least 60 percent. It varies from year-to-year a bit. As I mentioned, the other 40 percent are methods

development that may or may not have somebody from another center on them or some of them may be larger studies that actually are with other agencies as work that we're doing with, let's say, National Institute of Child Development, or perhaps EPA, or NIEHS or some other group.

DR. WATKINS: I'm asking a naïve question, but what's the total budget of the NCTR?

DR. SLIKKER: The total budget of NCTR— this year we're probably on a continued resolution, so this coming year's is probably going to look a lot like last year, which was in the range of about $58 million in allocated funds. The FDA allocated $58 million.

DR. WATKINS: And how much of that is flexible where you can actually shift or use it for new projects versus set salaries and keeping the lights on?

DR. SLIKKER: As you know, since you're a director of an institute, the majority of it is fairly set. It has to do with salaries. It has to do with keeping the place running because all of those funds have to support this facility and to maintain this facility.

But there still is a fraction, a reasonable fraction that is left to actually do the new studies and continue the existing studies, and to buy equipment and those things needed to explore new science.

DR. WATKINS: Is it 20 percent of the total budget? 5 percent?

DR. SLIKKER: Those are difficult questions to ask because of the way the budget is calculated for our studies. Each study's budget, the cost to run the finance and planning, as well as the animal and facility maintenance is incorporated into NCTR's financial plan.

We do our costing so each project maintains part of the Center activity but when referring to what's available for travel, for support of equipment and support of consumables, for example, that's a hard percentage to estimate. Jeanne do you have an estimate on that?

MS. ANSON: About 30 percent. There is a basic operational cost of the Center, and then we have dedicated funds for increased study requests and that's probably another 15 percent, which is dedicated to go into certain, specific research areas. The remaining percentage supports all of the contracts, projects, and whatnot within the center that are ongoing. Basically, our flexibility is probably about 20 percent or so.

DR. SLIKKER: By the time you have the contract costs incorporated in there to do the annual maintenance and the pathology in the building facility, it leaves very little to do that.

You also have to remember that these studies are usually three-year studies so in any given year you don't have that much flexibility because some of the money is going to have to go toward completing those studies that are ongoing. We add studies as we have both personnel and resources to maintain those studies. Does that help answer your question?

DR. WATKINS: Yes. Thanks.

DR. SLIKKER: Alright. Thank you.

DR. DOW-EDWARDS: In terms of interagency agreements and outside contracts and so forth, what proportion of your income—obviously it's above that $58 million—do you receive from these outside sources?

DR. SLIKKER: Diana, it varies from year to year, but it's been averaging at about 30 percent or so. The way I look at it is that other agencies and groups who create us, mainly through Inter-Agency Agreements, like our work so much because it's consistent with FDA's mission, which is one of the important goals here, so they fund us to do those studies.

In fact, some of the studies I've mentioned are done in conjunction with NIEHS and the National Toxicology Program. That's where a great deal of that funding comes from. So it's around 30 percent.

DR. SLIKKER: Any other questions? Alright, well thank you all very much. We'll go to the next step.

Agenda Item: Update from NCTR Divisions

Agenda Item: Division of Microbiology

DR. CERNIGLIA: I want to thank everyone for traveling from all different distances to be here this morning. What I'd like to do is give a brief overview of the Division of Microbiology and say who we are, what we've achieved, and how we've responded to the SAB reviews. That will be the essence of my presentation.

The Division of Microbiology has a two-fold function within the agency. First of all, we serve to perform fundamental and applied research in microbiology and areas of FDA's responsibility in toxicology.

Secondly, we respond to the microbial surveillance and diagnostic needs for the research project within NCTR and the FDA. I'll explain that in a moment.

The way we organize the program, and if you look at the way the SAB review has been set up, I must say that our program has been reviewed three times since I've been a division director at NCTR. The most recent was in 2007, and you all have that report and our response to that.

We're organized in these particular areas. One is in food safety and biosecurity, antimicrobial resistance, human microbiota and host interactions, environmental biotechnology, and the microbial surveillance and diagnostic support. I'll

briefly go over each of these subject areas and show how we've responded to the SAB review.

Our current research activities are organized in these five areas. One is developing rapid technologies, mainly in the molecular arena, to detect, identify, and characterize food-borne pathogens.

We've also been doing a considerable amount of research on mechanisms of resistance and variance of the pathogens that may enter the food supply.

Also, today I'll highlight some of our studies that are using the most current molecular approaches to monitor the interactions of the human intestinal microbiota and their interactions with antimicrobial agents, food contaminants, food additives, and probiotics. We have a series of projects funded by the Office of Women's Health, so we have studies impacting women's health too.

Lastly, in environmental biotechnology, we're improving environmental risk assessments of priority pollutants, including polycyclic aromatic hydrocarbons, and human and veterinary drugs by integrating systems biology approaches.

I was glad to see that Doctor Slikker got all of the numbers out there in terms of the budget so we shouldn't have those kinds of questions. But in terms of personnel, we have 41 staff, 28 FTEs and, as Doctor Slikker was mentioning, there is a

range of research scientists, fellows, support scientists, post-doctorate fellows, and we have three FDA commissioner fellows in our program.

When we were evaluated in our SAB, one of the things they noted, and I just wanted to make a point to say that we're continuing, is our consistency in terms of not only the number of publications, but the quality of publications we have been producing at NCTR.

The other aspect that was mentioned in the SAB is the visibility of the staff in terms of outreach at the national and international meetings and, again, this is just a snapshot of fiscal year 2010, but over 40 presentations were given by the staff at a wide range of meetings.

In fact, our major meeting is the American Society for Microbiology meeting. We had 19 presentations there. It's really exciting to see how our staff has interacted with microbiologists in the various research societies around the world.

In terms of the surveillance and diagnostic program, the SAB review didn't give a real critical, technical review because it's not really a research component; it's more of a support element of NCTR.

Our program, for those who are not familiar, has to assure that the animals are healthy and free from infection when

they are involved in the animal studies here at NCTR. We want to make sure the research data that comes out, whether it's the NTP projects or any of the other projects that are going on, is not compromised due to infections of the animals.

I'm sure that Doctor Carraway will be talking about our animal facilities here at NCTR and the various support elements later. They are very important in developing methods for the detection and identification of pathogenic agents. They also provide some support for research projects at NCTR.

What was mentioned in the SAB review is the fact that there is some succession planning. Don Paine, who is currently the head of the surveillance program, will be retiring shortly so during the SAB review, they wanted to make sure we had a plan in place to recruit. We did a nationwide search and we were quite successful in recruiting Doctor Sung G. Kim, who was head of the molecular diagnostic program at Cornell University.

You can see his scientific credentials and his job responsibilities at Cornell. He is going to be implementing some of these things and some of these changes within the diagnostic program at NCTR. We're really pleased, and I was really happy that Doctor Slikker let us transition so that we could bring him in; he is here now. He's been working for several months so there will be a really good transition when Don leaves.

In terms of our food safety and research program at NCTR, and I'm really thrilled today to know that we have the Office of Foods represented here, most of our projects collaborate with ORA, CVM, and CFSAN.

Basically, we have projects in several different areas. One, we call surveillance monitoring, just uses a wide variety of techniques to detect food-borne pathogens in the marketplace. We also have a lot of methodology in the phenotypic and genotypic characterization of food-borne pathogens.

Thirdly, we have projects with the Department of Homeland Security and other government agencies and I'll mention that in a moment. We also hired a virologist, which I'll mention in a little bit, too. So we have a virology program, which was initiated in food safety. Also, we have collaborated across NCTR and other FDA centers in bioinformatics databases which you may hear about from the other speakers later.

The project I'd like to highlight because there was as lot of discussion in the SAB report is the one we had with Homeland Security and the USDA. Doctor Syed Khan led that program in the laboratories.

The idea behind the study was driven by the concern from the Department of Homeland Security after 9/11 about the vulnerability of our food supply because it's centralized. We

were very concerned about certain commodities like hamburgers, milk, liquefied egg products, et cetera.

In the program, the funding we received was used for liquefied egg products. We looked at the survivability of bacillus anthracis in a wide variety of liquid egg products. As you can see, we completed and published a number of studies looking at egg yolk, egg whites, and whole eggs.

One of the questions that came up in the SAB review was the issue of the inactivation of bacillus anthracis in this matrix with the egg whites and the mechanism of that inactivation.

Doctor Syed Khan and a group did an excellent job of finding out the lysozyme in the egg white that was very important in the activation. This research was just recently presented and highlighted by MSN and picked up by news organizations. You can read it yourself--Syed Khan, researcher at NCTR, so we got good press in how the application of this particularly works in possibly combating a bioterrorist event.

This was interesting. We are working very carefully now on applying this technology of a lysozyme inactivation of bacillus anthracis in a variety of other matrices besides liquefied egg, like hamburger, et cetera.

Another aspect of the SAB review, if you have had a chance to read the report, is that we also needed to recruit a

senior investigator to take the lead in food safety. I'm pleased to announce that we hired Doctor Steve Foley, who has been very active since he arrived. In fact, he represents NCTR in the research component with Doctor Tom Flammang in the Office of Food Science Technology and Research Integration core group. We're very pleased, and his research program is also getting off the ground quite nicely, too. We followed up on that recommendation.

We also followed up on the recommendation of hiring a virologist in the program. I'm also pleased to say that in all of these examples we've done competitive searches in getting the top people. In fact, each person I've mentioned so far was my top choice. I'm very thrilled they decided to come to NCTR.

We hired Doctor Marli Azevedo from Ohio State University to get this virology program going. Again, she's done an excellent job of getting involved within the agency. She's on the virology working group across the agency. As you can see from the title of these various ongoing projects, she has interactions with various FDA centers, including CDER, CDRH, and CFSAN.

Again, I just want to emphasize that we do listen to the SAB committee and we try to respond accordingly to the inputs we get.

In terms of antimicrobial resistance, our program covers across the FDA with the other FDA centers. This is such a hot topic. But at the same time we do have some unique aspects to our program.

First of all, we have projects where we can actually look at the antibiotic residues and how they impact the human microbiota. No one in the agency is doing that type of research. We have also been doing a lot of work on getting better methods to rapidly detect the antibiotic-resisting gene in a population.

Thirdly, we have this farm to fork clinic where we have actually been doing studies in the field, like in Fayetteville, Arkansas, where there is a large area of poultry facilities so we can actually track the dissemination of antibiotic-resisting genes.

Also, we can look at the metabolism of antibiotics in the environment, an emerging area of pharmaceuticals in the environment. We’ve all seen the reports of worrying about what’s in our drinking water, et cetera.

I think our program is interesting in the fact that we can look at what goes in, such as if you ingest the residue, we can look at what goes out, the degradation of it, and we can look at what’s in between.

The other unique area is human microbiota in host interactions. Again, these interactions are such a big field

now. I think you've all, with the beginning of the Human Microbiome Project at NIH, put a lot of money in, and seen papers coming out on the linkage of the human microbiota in host physiology and host health, whether it's diabetes, nutritional deficiencies, Crohn's disease or irritable bowel disease.

We're very carefully looking at this from more of a toxicological perspective-- that the science would be our particular niche. What we've done historically is looked at various factors, whether it's azo dyes, food contaminants, dietary supplements, probiotic products, antibiotics, and how they impact the human microbiota.

It's very interesting when you actually look at the microbiota because we know that there are trillions of bacterial cells in our gut. We also know from a genetic repertoire of potential that there's at least two times the amount of genetic information in the gut compared to the human genome. It's quite a fascinating area to work in and at this moment we're looking very carefully at these interactions based on our strengths here at NCTR, and also the needs of the FDA Centers.

One area, which I'd like to highlight because there is an enormous regulatory impact, is the impact of antimicrobial residues on the human gastrointestinal tract microbiota. To those who are familiar with this area, it's the fact that antimicrobial agents are used in food-producing animals for both

sub-therapeutic and therapeutic uses, so there's always the potential that these residues, if the withdrawal times are not adhered to, could end up in our food supply. If we ingest those residues how do they impact the microbiota?

The human health impact is the fact of cross-resistance. If these drugs are very similar in chemical structure and also in the spectrum of activity, then the point is that they may not be useful if we do get resistance in the gut due to these drugs used by animals.

We've been working very carefully at the global level, with the World Health Organization, and we've also been working very closely with the Center for Veterinary Medicine, as well as with the VICH, which is an international harmonization committee on expert working groups. In fact, I have meetings on Monday and Tuesday in Washington on this particular subject.

We're providing information on really understanding this interaction of the food that contains the fluoroquinolone enrofloxacin in this particular case, to see where it gets metabolized if it gets in the gut. In this particular case it can get de-ethylated to ciprofloxacin. So you have an animal drug actually being metabolized to a human drug. This gets into the cross-resistance issue.

We actually have model systems that we've developed. In the SAB report they asked us to spend more time on validation

of these models and that's what I'm going to talk about, along with some of these critical issues.

We're using the latest technologies to do this. It's a pretty exciting time now. I think in 1995, the first microbial genome was done. In 2010, now we know that 3,000 genomes have been sequenced and if you actually project out to 2020, about 1 million genomes should be done.

There's an enormous amount of information. There's an enormous amount of technology. We're using these technologies to solve this problem. I know you're going to hear a lot about personalized nutrition in medicine from Doctor Kaput.

One thing that is very interesting to us is that we know each one of our human intestinal microbiota is very unique. We know that know. We do a lot of studies. One of the things on this committee is how many do you really want to analyze when you're doing it? How many volunteers do you need in a study?

We're doing these latest techniques of DDG analysis, pyrosequencing, RT-PCR, et cetera, in putting this all in to get out this issue. One point that I would like to make where we're spending a lot of time that reflects on the SAB is really understanding when we ingest these residues, when it goes into the GI tract is it really bioavailable?

What we know with this particular data is that as you go down the GI tract, the microbiota actually changes because

the water content in the GI tract changes, so there's a difference between bacteria that are associated on particles versus bacteria that are freely associated.

We actually have the experimental evidence to prove that, which you can see by doing pyrosequencing analysis. We're working hard to solve that.

We also have three projects in the Office of Women's Health. I know Doctor Beverly Lyn-Cook will be talking about this today so I also want to thank her for her efforts in helping us get these projects through the system.

We have one project on the human microbiome in terms of a skin microbiome, cosmetic microbiology issues, and we have two on the vagina microbiome—one on toxic shock syndrome with staph aureus and the other on yeast infections.

We're very active in environmental biotechnology with the crude oil spill. We've done a considerable amount of work on polycyclic aromatic hydrocarbon degradation.

We're leaders in the world in this particular area, it's well noted in the report, and we've done the systems biology approach where we've linked all of this. All I wanted to say is we're the first laboratory in the world now to actually know exactly molecules like pyrene, which is very similar in structure to the highly carcinogenic benzo(a)pyrene.

We know every enzyme and gene, and also every metabolite that has been formed by this particular organism. This was all based on getting genome sequences. We had five bugs sequenced with funding from a grant with DOE Utah State University.

We're using this information to become experts with polycyclic aromatic hydrocarbons. We have two ongoing projects. One is with Dauphin Island Lab, which is a Gulf Coast seafood lab of CFSAN, looking at the interrelationship of hydrocarbon degradation in the oyster itself, and also in the environment around the oyster. Does this exacerbate pathogenicity because we now like vibrio vulnificus, and could these types of things interact?

We're interested in actually knowing the derivative potential of this, and also of the bugs that are related to the oyster habit and community.

With that, I just wanted to thank everyone. I won't be staying for these other presentations so I wanted to let my colleagues know that I'm not running out because I'm not interested but at 9:40 I have to give a talk to this Congressional Committee. Thank you very much.

DR. AFSHARI: So we have just two minutes here for questions.

DR. BURCHIEL: I'm curious about how you characterize the host interaction with the microbes. What are you doing, say, looking at adaptive and innate immune system?

Dr. CERNIGLIA: Actually I do have this slide but I won't keep going through it. We just hired a person, who I'm really thrilled to have her join our program. She's from Texas A&M University. She has expertise in immunology and gut immunology, so we're hoping to get into these areas. At this time we haven't gotten into that.

DR. SPEILBERG: I'm curious and interested in the change in flora in the microbiome and genome, not so much in the general population, but in those who have an infectious disease, such as diverticulitis, appendicitis, overt disease processes, that we treat often with things like ciprofloxacin and metronidazol.

Is there any effort to take this thinking out into the general gastroenterology community looking at acute GI infectious disease and see if, in fact, some of the hypotheses that you suggest really do have an impact on the prevalence of those diseases, the prevalence of resistant organisms, as well as our difficulty in treating them?

DR. WATKINS: I don't know of research that's directly looking at that. Diverticulitis is an example where the flora,

itself, is the source of the infection as opposed to food poisoning or things like that.

I know of work that Dr. Relman at Stanford has done, looking at the effects of recurrent antibiotic treatment in cohorts of people to see if you could revert back to your old pattern. I've seen him present some of that and the answer is that you do, but over time you can drift to a whole different thing. But I haven't seen the tie-in to infectious disease.

DR. SPEILBERG: You really wonder if the hypothesis is true that exposure to residues is shifting gut flora, and that the diseases we treat may, in fact, be due to different organisms or at least potentially resistant organisms, which could be a nightmare down the line given the prevalence of diverticulitis in the population.

DR CERNIGLIA: I'd like to make one comment. You're absolutely right. There's a lot of work out there now Doctor Speilberg, and certainly Jeff Gordon's group, and you can see a series of studies that have been done where they're looking at the microbial populations in the bacterial diversity certainly used in high throughput pyrosequencing.

I think a lot more work needs to be done to find whether there are linkages or not. I don't know if we over-hyped it or it's actually a fact. I think that we have to be careful. Even in obesity, you'll see obesogenic bacteria classifying.

That's cool, but as a microbiologist, whether it really means anything or not, I think, still needs to be carefully determined.

I admire the work that's being done because it is excellent and there are pioneers in this field. They've really set the stage for a lot more work that's out there. I hope that NIH continues to fund this kind of work because there is concern now that we're at this threshold and whether this can be maintained.

DR. AFSHARI: Thanks Carl. I think we're going to have to move on. I'll just remind the Center Directors here, if you didn't get a chance to put your comments in, please do about this division in your comments this afternoon. Thank you.

Agenda Item: Division of Biochemical Toxicology

DR. BELAND: I'm Fred Beland; I'm the Division Director for Biochemical Toxicology. I'm going to spend the next 15 minutes giving you an overview in the manner that Carl did, but I won't have slides as technical as his.

As Carl said, we do fundamental applied research but we, in our division, do toxicological assessments. We do a lot of bioassay work, but at the same time we do mechanistic studies so that we can determine whether or not what we're seeing in an animal has any relevance to human. It's a lot of bioassay. The

other thing that is invariably ongoing is tied to a regulatory need of the FDA.

There are three general areas in which we work. A lot of our funding from our division budget last year, discretionary budget, which is travel supplies and equipment, was about $2 million. About half of that was funding from the NIEHS through the National Toxicology Program.

Likewise, about 50 percent of our research effort as far as charging time is to the NIEHS and NTP. These are compounds nominated by Product Centers to do the bioassay work here, and also the mechanistic studies.

Another area, just like Carl mentioned, was food safety. This goes into the NTP effort. For instance, we’ve done acrylamide, we’ve done dietary supplements, but there’s also FDA funding for this.

The third area is epigenetic mechanisms of carcinogenesis. We have a long history of looking at genotoxicity. We collaborate with people in, what I call, genetic toxicology—it has a different name at the moment.

We’re interested in cancer. We’re interested in historically, based upon formation of DNA adducts, but then we’ve also come to the realization that there is a very significant epigenetic component to these so we have a very large group working in this area. We interact with them when we

do the bioassay work with the mechanistic studies on epigenetic components.

We have twelve research groups. For those of you, and I'm listing the team leaders here, the total division varies, but it has around 50 people at the present time. Post-docs come and go. We have visiting scientists. So, typically we have around 50 people.

We have twelve independent team leaders. For those of you, some of you are new, who were here a year ago and heard me speak, but the difference is that we have three new group leaders.

One is Matthew Bryant, who I'll talk about more a little bit later. Jeff Fisher has also joined us. Bill Slikker mentioned him earlier. The third person is Lei Guo, the third person down from the end, on the right hand side.

Lei Guo was a member of Systems Biology but we have certain needs within our division, and her expertise seemed to be better aligned with what we were doing as opposed to Systems Biology. So at the first of the year she moved to our division and is heading up an NTP effort. As far as accomplishments I guess I can count it in papers. That's what I've always kind of done. There are other metrics, of course, but we have a document tracking system. We have this very elaborate process compared to universities for getting a manuscript out of this place.

We do have a very good document tracking system. These are peer-reviewed manuscripts that were accepted during fiscal year 2010, so from last October through this October. I think it's a very good rate of productivity.

We also have four NTP final reports. These are, as the person from NIEHS can well testify, really tedious things to do. They are GLP studies, and on top of that, there are multiple layers of review.

I'd like to briefly discuss three of our papers because I think it gives a flavor of what we do and why it's important to the FDA and so forth. Then I'll just briefly tell you about the NTP reports.

The first paper is about an effort directed by Dan Doerge. It came out in Toxicology and Applied Pharmacology. It's about Bisphenol A. Bisphenol A is going to be the death of us.

There's a huge controversy regarding Bisphenol A, and part of the reason is because even though there have been lots of studies, studies are underpowered and the analytical methods haven't been very good.

Dan looked at the concentrations for the blood levels of free Bisphenol A. When active, this compound binds to the estrogen receptor and is metabolized to a glucuronide. It's very important that you measure both. If you just measure free BPA, it's not going to tell you the whole story.

We administered deuterated BPA because of the background levels. Everybody has BPA in them. So if you really want to know what's going on, you have to use it at a stable level. In doing this, he could demonstrate, quite convincingly, that BPA is glucuronidated very quickly. The ratio between free BPA and the glucuronide is about at least one hundred to one, if not greater.

There is concern about infants. Infants don't glucuronide at the extent of adults, but it's still very good. As a result, serum levels of these animals were about one nanomole. Now, this is about ten deferred away from the ED50 for the estrogen receptor for BPA.

What that implies is that these are very low levels. It also implies that if people are going to go out and measure BPA they need to measure both BPA and the glucuronide, because if they're not finding a big differential then there's something wrong with their analytical method.

I think this has tremendous regulatory impact because there are lots of people who are saying we are exposed to massive quantities of BPA. I honestly don't think it's true because they have not done their analytical measurements properly.

The second paper I'd like to emphasize has been submitted to Toxicological Sciences. It has undergone review and

I think it’s going to be accepted. The lead scientist on this is Goncalo Gamboa da Costa. The analytical work was performed by a very good post-doctorate fellow, Cristina Jacob who, unfortunately, decided to go back to France.

We had collaboration with universities for the first paper. Here you will see we have collaboration with other FDA Centers.

The idea behind this paper was the pet food crisis where pets were exposed to melamine due to adulteration of pet food. Then, in China there was infant formula that was adulterated with melamine.

This is not reagent grade melamine. Most people would be exposed to scrap melamine. Scrap melamine contains melamine but also contains melamine that is a tri-amino derivative. Also, those amines can be converted to oxygen and you can get to cyanuric acid.

People are being exposed to both based on the FDA risk assessment, other risk assessments were based on just melamine, which is actually not very toxic by itself. You put the two together and you end up with this beautiful crystal lattice in the kidneys—I mean beautiful for a crystal that happens to be in the kidneys.

We have done dose-response studies. We have done benchmark-dose modeling. What we’ve been able to demonstrate in

this paper is that current risk assessments are probably between two- and ten-fold too high. The actual margin of safety is worse than the current risk assessment.

Now we're doing additional studies where we do a seven day exposure. We're going to do a 28 day exposure, and it appears to be even worse. Again, I think this is important for the FDA to develop proper risk assessment.

The third paper I'd like to mention was an effort directed by Barry Delclos. It has to do with this huge endocrine disruption effort that we've had here at NCTR. I bring this up because this paper was selected by the European Toxicology Society as the outstanding paper of the year.

Barry was invited to go to Barcelona. He made a presentation. The other thing I'd like to emphasize is that in the first paper we had collaboration with universities, the second paper was a collaboration of other FDA Centers, and here we show collaboration with another federal agency.

As far as final reports go, we've finished aloe vera. This is an oral study. By finished, I mean the NCTR reports exist. We're in the process of finalizing the NTP reports. These will be presented in the spring of this year.

This is oral aloe vera. You always think of topical aloe vera for burns and so forth. Oral aloe vera is readily available and we demonstrate, quite convincingly, that it's a

colon carcinogen. If you take whole aloe and grind it up, which is a product that is on the market, it's a colon carcinogen in rats. There's no question about it.

Acrylamide was the issue—the Swedes found it in potato chips and French fries and so forth. We've completed that. It's quite clearly a multi-organ carcinogen in both mice and rats. If you do benchmark-dose modeling, I'm convinced that it actually does make a significant contribution to the etiology of human cancer. It is clearly much greater than oral exposure to benzopyrene or to heterocyclic amines.

The reason the epidemiologists haven't been able to isolate this effect is because everyone is exposed. You don't have a control group that's not exposed to acrylamide. Everybody is exposed to acrylamide. It is a very potent carcinogen.

Retinyl palmitate was part of the phototoxicity study. Bill Slikker mentioned the far right hand side of the center is a phototox facility. I would classify it as not a very potent carcinogen—we're talking about coal carcinogenicity now. We're looking at what retinyl palmitate does in the presence of light. My feeling, this is not FDA policy, is that it's really not very potent.

We're finishing a report on transplacental exposure to antiretroviral drugs. The idea here is that women who are pregnant take these drugs to prevent the transmission of the

virus, but what happens to their babies? Do babies have an increased risk for cancer?

The basic conclusion from the model we're using is that there wasn't much induction of cancer with the exception of perhaps the mixtures that contain nevirapine, which is a non-nucleoside analogue in a reverse transcriptase inhibitor.

Studies that we're currently doing are long studies. We have some we're in the process of starting. We don't change direction very quickly.

We have a large study with Bisphenol A. It's a 90-day GLP study. People are reporting problems with Bisphenol A but are a result of underpowered studies. They are not GLP studies, so when we're done, we want to present a package where people can believe the data.

At the same time we're doing DEHP. The issue with Bisphenol A is oral exposure. The issue with DEHP is IV exposure because people who have the highest exposure to DEHP are infants in the neonatal intensive care units. They have a very substantial amount of it.

Usually, we would get criticized for doing an IV study but it is worth it to actually show the differences in toxicity of oral as opposed to IV administration in mouse models.

We're continuing the work with melamine and cyanuric acid. We are going to set up a 90-day study. I imagine it's going to go onto a 2-year study.

We're doing studies on furan. Furan is another dietary carcinogen. Interestingly, furan causes cholangiocarcinoma in rats, but we cannot do a risk assessment because the previous study showed 100 percent incidence even at the lowest dose. So we're putting together a study to have an absolutely beautiful dose-response. At the same time, we're doing mechanistic studies in pharmacokinetics.

Nanosilver, part of, as Bill Slikker mentioned, our nanotechnology effort. Nanosilver is in a lot of products so we're looking at the oral administration of nanosilver. These studies have just started. I have to stop? Okay.

DR. AFSHARI: We have time for questions.

DR. BELAND: Okay.

DR. AFSHARI: You can just read the rest and we'll have two minutes for questions.

DR. BELAND: Okay. Triclosan is a product that's used dermally. The problem is its phototoxicity because under UV light it can be converted into dichloro- and trichloro-furan derivatives, which of course are not good. We have no idea if this occurs outside the test tube. The question is does it occur in animals?

And, finally, aloe vera. The aloe vera industry is not particularly happy with us since we've shown that it is a colon carcinogen. What they are maintaining is that we are using the wrong material. We initially proposed to use products that were just the gel and charcoal-treated material. This was stopped after a 14-day study, but now we're going to go back to repeat all of that.

DR. AFSHARI: I'd like to open it up for questions from the SAB.

DR. WATKINS: You actually get money from the EPA?

DR. BELAND: No. NIEHS.

DR. WATKINS: NIEHS. Sorry. How much money?

DR. BELAND: Paul Howard could address that. The interagency agreement is typically somewhere between $10 million and $15 million a year.

DR. WATKINS: Is that renewed each year, or do you get like five years?

DR. BELAND: It's like our budget- just as NCTR's budget is done on a yearly basis. You don't get money for five years. Presumably, if you start a bioassay you're not going to go beyond those after one year. It's been in place, I believe, for 15 years now. As long as they're happy with what we produce there's no sign that it's going to go away.

DR. HINES: Fred, a lot of the issues are extrapolation to humans, and I know a lot of the studies that you do are based in rodents. We do have the capacity to extrapolate a lot of the computational methods to humans. Are you implementing a lot of those approaches?

DR. BELAND: If I had gotten to my next slide, yes. I was going to point out one of the recommendations of the Science Advisory Board we followed to do more toxicokinetics and pharmacokinetics.

We had a fellow work with us named John Young. He retired. We went out and recruited Jeff Fisher, and Jeff Fisher was a Professor a number of years. He was a department chair of the Department of Environmental Sciences at Georgia. He joined us in July and he’s bringing that expertise. He’s in the process of recruiting two post-doctoral fellows.

The work that Dan Doerge does, the work that Goncalo Gamboa da Costa does, s is all developing and measuring levels in plasma and so forth, but we want to then take the modeling step where we go from the animal to gather as much human data as possible.

Dan Doerge is starting to do measurements of Bisphenol A in humans. Any data that we can acquire will then be used by Jeff Fisher to make these extrapolations.

DR. YAGER: I'm just curious as to how aloe vera was nominated for these studies—just quickly what the background was on that?

DR. BELAND: Aloe vera was nominated by the National Cancer Institute because it has anthraquinones. They felt that the level of exposure was very high. We've also did it topically and orally. Topically it didn't do very much, but orally it's pretty nasty.

Now what we don't know is whether we use the whole leaf preparation or not, which contains anthraquinones, because we want to know if the response we see is due to the anthraquinones. So we're going to come back and take a charcoal-filtered preparation and at least do 90-day studies because you can very clearly see what's going on after 90 days.

DR. BROACH: This is a question that also applies to the other divisions as well. You obviously have lots of projects you could do, and you've listed a number of them that you have done. But what is the process by which you rank order the things that you do and the things that you don't do?

DR. BELAND: As I said, a lot of our stuff is driven by the nominations by the product centers as specific agents to test under the NTP funding.

I have discussions with Paul Howard to see whether or not we have the expertise within a division to do the work, and

then if we do, what persons—I mentioned Lei Guo came from another division to take over responsibility for one of these.

There are compounds being considered at the moment that we simply don't have the resources to do, both from within the division. Plus, we also have to take into consideration our pathology capabilities and our animal husbandry capabilities. There are limits to what we can do at the moment.

As far as investigator-driven studies, we attempt to get funding from the Office of Women's Health. There was some food money. We also have the National Cancer Institute pay for a portion of our epigenetic research. We have a cooperative research and development act with the University of Illinois that brings in money to look at "endocrine-disrupting compounds."

DR. AFSHARI: Thank you Dr. Beland. I'd like to move on now to the Division of Systems Biology.

Agenda Item: Division of Systems Biology

DR. MENDRICK: I would like to update you on what we've been doing since the last meeting, how to provide an overview for people that are new, as well as address recent comments from our SAB review. So let's see how well I do.

As Bill mentioned, one of the things I did was rename the division. There are several reasons. First of all, as Bill mentioned, in this division we're looking at things other than

classical toxicity. We're looking at disease processes. In some cases we're looking at efficacy.

In the more global sense, I have found that some people have very narrow views of what toxicology means. For example, a past colleague of mine thought there was something magical about toxicity biomarkers and that they had no relation, whatsoever, with disease biomarkers.

We would try to use the example of ALT, BUN, and somehow we had this mindset that these were magical and had no use to him as a clinician. There is certainly so much crosstalk between biology, which is why I opened the name to embrace what we're already doing and maybe get people passed this concept of toxicity as only related to X.

In my division, we're looking at obviously increasing the effectiveness of regulatory science. The interesting thing in this division is that we have a very multidisciplinary team. We have bioinformaticians, biologists, analytical chemists, et cetera, and hopefully they will all work together on the projects where we have the need to collaborate.

The easiest thing would be to throw all of this expertise at every project. That doesn't make any sense. There's always a balancing act to determine which expertise is needed for each project.

One of the things that did come out of our SAB review was to find a better way to balance it. We're working on this and I meet with the leading members of my division often to talk about the various projects and try to get feedback from each other.

We do embrace many different things. A large number of us are looking at translational biomarkers, again related to both disease and safety of FDA-regulated projects.

We are also looking at developing innovative tools to improve detection of food contamination, identification of infectious diseases, and the diagnostic procedures. Weida Tong is doing a lot of work looking at bioinformatics solutions to facilitate the regulatory process.

These are the people who run the Centers of Excellence within my division. It's divided into six centers. If you have follow up questions you can seek them out and ask them.

We had the various OMICs centers, as well as centers focused specifically on liver injury because that's still a major problem for drugs. As Bill mentioned, we have an innovative technology group and, again, we have Weida Tong in bioinformatics.

The interesting and challenging parts of this job are the different types of technology and expertise available—science is no longer one-dimensional. We don't have that ability

for one-dimensional science anymore because we need to bring so many different types of expertise to the table. How do you mix and match and get people working together on important projects?

I'm going to very briefly discuss some selective projects because of time. I can't talk about everything we're doing, but I'm going to talk about biomarkers looking at drug toxicity and disease, bioinformatics, some efforts being done on food contamination, and improving diagnostic procedures.

On the biomarker side I'm going to focus on a number of initiatives looking at liver toxicity. I don't have time to go into this today but we're also working on cardiotoxicity, for example Joan Fusco's group in genomics is doing a cardiotoxicity project. Rick Beger in metabolomics is doing nephrotoxicity projects. Today I'm going to focus on the liver.

One of the major problems I see is that you have clinicians on one side and you have people who focus on the preclinical environment, and they never get together and talk to each other. That's true in the regulatory agencies, it's true in academia, and it's true in pharmaceutical companies. I don't understand it.

I've been here for two years. One of the first things I did was convened what we called a "hepatotoxicity working group" where we have people that are more focused on the

clinical aspect of liver injury. Paul Watkins is a member of this, as are some people from the FDA, and academia, et cetera.

We also have people that focus on the preclinical side. We get together and we discuss what the issues are, and we may determine that the biomarkers you need on the preclinical side may have no relationship to the clinical side and vice versa. But as a PhD, and I came from a clinical environment at Harvard, it was very easy to come up with really great ideas and find out that for the clinician, it had no relevance to what they needed. It’s important to get these groups talking.

We have some animal studies on the liver that apply multiple OMIC technologies. We have a knowledge base we’re working on. We’re working on bioimaging and also doing in silico modeling. Again, these are just some examples.

We’re doing a study in animals where we’re looking at OMICs in the liver. We’re looking in the blood. We’re looking in the urine. We’re using a multiple OMICs approach, and the idea is to try to identify better biomarkers that help in the preclinical side in identifying potential hepatotoxins. Whether or not these prove useful in the clinical side, we won’t know until we see what we find. This is focusing mostly on the preclinical side.

We’re looking at the liver, circulating blood cells, body fluids, micro-RNA, message RNA, proteins, metabolites, and

we already, as I mentioned, have a hepatotoxicity working group we're working with that is helping us on this project.

I don't want to infer that the hepatotoxicity working group agrees with everything we're doing. I deliberately got an eclectic group together, so Paul can chime in if he wants. But we're trying to make sure we're addressing important needs.

Weida Tong is running a liver toxicity knowledge base. The idea here is to use in silico data. There are a lot of databases out there. The first thing they did was mine public databases and get information on the chemical structure of a drug, the Pk information, histopathology reported in humans, what the drugs is used therapeutically for, and combined all this information with some of the data we've developed from the rat models. They've been running some primary hepatocytes. He's going to be doing some non-human primate work with some collaborators in China to actually start to try to validate what he's pulling in from the public domain. This will be publicly accessible when it's done.

The concept is to be able to enable reviewers and researchers to look at hypotheses if a new drug comes at you or some other mechanism, and try to see what you can pull in from all this public domain information and new research. We're also looking at combining a basic metabolomics approach with an image approach.

So Rick Beger, who has a metabolomics group, has already published a paper where you can use metabolomics on body fluids. You can pulse with a non-radioactive isotype of glucose, and then you can follow the different metabolites of glucose as it goes through, for example, this particular cycle.

The benefit of metabolomics is that sampling body fluids is not invasive. The downside of body fluid metabolomics is that you have to infer where it’s coming from. So part of the advantage is using this approach but coupling it with bioimaging so you really are looking at the organ.

In this collaboration he’s working with Sergey Levchenko, who’s in neurotox, as well as William Salminen who’s in our hepatotoxicity group. They are doing a pilot study in rats where they are trying to see if you can visualize liver injury and dysfunction.

We’ve been waiting for probes and the study hasn’t been done yet, but they are going to use C-13 glucose to look at the flux and see what happens over that chain. They are going to use usnic acid, which is a dietary supplement that has been shown to affect energy metabolism in the liver. They’re going to look at cystine fluxes after treatment with acetaminophen. It’s well known that acetaminophen affects the self hydro containing compounds in the liver.

The benefit of this is that it’s non-invasive. You can repeat the same individuals over time. If it proves useful, it clearly has a clinical relevance so we could move it to the clinic.

The question we had more recently in the hepatotoxicity working group meeting a few weeks ago was if a clinician would want to use this kind of information? In what clinical situation would they find this kind of information useful? So, again, we want to make sure we are focusing on the right directions.

A bunch of PhDs aren’t just sitting in a room going, I bet they’d use it for X. Then you find out they can’t justify it to the insurance company to pay for the test.

One of the things, for example, we talked about is the issue of looking at liver fibrosis and some areas that might be, particularly in the clinical realm, difficult to look at, and where they felt it justified this kind of imaging technology.

Another effort we have is looking at *in silico* modeling. It’s being run by Leming Shi?) and the bioinformatics group. It’s actually a collaboration we have ongoing with CDER. Janet Woodcock has been involved in this because she also has a laboratory within CDER, and she’s actually providing a little bit of funds for it on this side. Michael Norcross is doing the laboratory validation within CDER.

On this side we're looking at an *in silico* approach. It would be related to personalized medicine. You would use three-dimensional information of a particular drug and unique HLA protein variance to see if the drug is actually directly interacting with an HLA molecule.

There are well known examples of very particular genotypes that have been shown to be responsible for some adverse events in genetic issue. In fact, Doctor Yang has joined Leming Shi and he's working here on this now. We're trying to see if you can predict if using an *in silico* method for the ones we already known have this association, and then if we can use it to predict future ones.

They have a pilot study underway with 69 HLA protein variants and 35 drugs. It was a little bit slow until we got access to the CDRH supercomputer because it's obviously very computer intensive. So far the preliminary data looks promising but clearly there's a lot more work that would need to be done.

Again, the benefit if this worked would be the ability to predict adverse reactions a patient with a particular type of HLA molecule may experience from a new drug molecule. You wouldn't even have to expose a person to a drug. You could determine that up front.

To summarize, we're using a multi-faceted approach to hepatotoxicity. We're looking at OMICs in rats. We're looking at

combining public knowledge compiled with new *in vitro* and *in vivo* experiments. We're looking at bioimaging with metabolic flux and using *in silico* modeling approaches. We are using all the different types of expertise from the division and applying it to one common problem.

Another aspect the division has been very involved in, particularly Leming Shi and Weida Tong, is looking at forming a consortium called the Micro Quality Control Consortium and addressing some of the issues that, to date, are mostly dealing with micro array genomics.

The most recent effort they had, which they have almost finished, is MAQC-2. This came up because the literature unfortunately continues to show examples where molecular signatures that people had found, particularly in the clinic, don't replicate.

A paper from 2005 talked about the fact that when they looked at some of the studies and literature, five out of seven of them didn't classify patients better than chance.

A more recent problem arose at Duke University where investigators used what they thought was gene expression information looking at the NIC-60 cell line in response to different therapeutic agents. They were then running a clinical trial looking at the patient's tumors and trying to guess which drug would work best on which patient.

Some bioinformaticians and biostaticians in Texas kept pointing out that there were some basic problems with the data and the way it had been analyzed to the point where they actually felt patients were being put at risk. When this type of information is in the public domain, any relatively new technology has to worry because it can set the whole field back.

The timing was very good for the MAQC-2 summary. They just came out with 11 papers in August of this year. In two different journals, there is going to be a special edition—both are a nature publishing group. It had 200 participants from 86 organizations—the very public forum.

What they found, briefly, is that it’s not as important which mathematical statistical approach you use. What’s more important is the way you statistically validate the model, as well as some of the laboratory issues, such as the batch effects, the knowledge of the personnel running the experiments, et cetera, and that has a lot to do with some of the issues that have been present in the literature. The question they are going to address soon is if it will affect an FDA regulatory guidance document.

ArrayTrack is another technology that has come out of Weida Tong’s group. Again, I think many of you know about it. There’s a lot of information. Because of time I won’t go through a lot of it. It’s been used in the voluntary genomic data

submission process at CDER. People inside the FDA use it. People outside use it. It’s freely available on the internet.

Another completely different program we have here is looking at detection of pathogenic bacteria. This is being done by Dan Buzatu and John Wilkes in the Center of Innovative Technologies. The concept was addressing a fast assay for detecting bacterial contamination either in food or on surfaces.

It was assayed through the Arkansas Department of Health, and it passed the validation test for FERN level 2 looking at E. coli 0157:H7. It works on a number of very complicated food matrices that don’t work on some of the current testing paradigms. Again, it’s extremely sensitive and very fast.

Most recently, there’s been a lot of interest in this by commercial entities. The Rapid-B was licensed out through CRADA to a local company, and we’ve had multiple conversations with people in other regulatory centers about what their needs might by. If you have a testing platform that can identify bacterial contamination where would you want to use it? Could you use it? What areas? CBM, apparently an issue is feed for animals. They know it was bacterial contamination. What kind is it, et cetera?

The work is going to continue to expand to relevant species. We’re working to see if we can modify this and actually

detect viruses in food, biologics, and other areas. Again, I'm sure Dan and John can answer more questions if you have them.

Another thing Dan and John have been interested in improving with Rick Beger is looking at diagnostic procedures. Unfortunately, right now if brain cancer is suspected you are subjected to an MRI, and then they do a brain biopsy, which has a fair amount of morbidity and mortality associated with it.

They approached this using their pattern matching expertise because of their mass spec background, and they developed a new algorithm that can identify nine types of brain lesions with 95 percent accuracy by looking at the spectral data that comes out of an MRI. A paper just recently hit a publication and they have filed a patent.

We've expanded the clinicians we're in contact with. This got started by a radiologist and we now have Sunder Rajan involved, who is at CDRH as an MRI expert. We have a neural surgeon at Johns Hopkins who was actually a CDRH review. He's gone back to be a neural surgeon at Johns Hopkins. We're trying to get an additional radiologist and oncologist involved.

Again, what we find is that different clinicians have different questions they need answered, so what question one specialty needs, and what question another specialty needs may be different.

We'll move to additional tissues as it seems reasonable to do so right now—the focus is on the brain. Trying to wrap this up quickly we're going to continue to address the need for new biomarkers. The hepatotoxicity working group is helping to define the clinical needs. Again, we had a conversation a few weeks ago about what is a clinic need and what can we do to try to find better systems to both predict and manage patients that have DILI, an other liver injury.

We need to obtain more MRI data of the brain to develop new models based on additional clinician feedback. Again, we're going to be working with Sunder Rajan to try to help secure some more of this data.

The next version of the MAQC-2 is looking at next generation sequencing. There are a lot of different platforms that are ever-changing out there, and yet the FDA is already obtaining sequencing data coming into the regulators. So we're trying to help run a public consortium and identify some of the issues surrounding that.

One of the things we're continuing to do is meet regularly with members of the various regulatory Centers with the FDA. I want to make sure what we are doing is relevant to your needs. In fact, I'm tracking that within the division so if there's suddenly a dip I'm going to know about it. I want to make sure we have constant communication to get feedback to make

sure what we're doing is relevant to the FDA and public health.

Again, I just focused on a few things. We have a lot of other work being done in some of these areas that I didn't have time to talk about. I welcome questions.

PARTICIPANT: I just had one comment I wanted to mention. I was interested to hear about the *in silico* modeling project that you have with Mike Norcross. Just as an FYI we have a similar type of effort because of, for example, recombinant factor 8, and the development of inhibitors in certain populations. So we're looking also at modeling HLA interactions and whether or not we can predict those kinds of things.

PARTICIPANT:I was interested in your HLA study, and I was curious if you're doing any such effort preclinically, and also looking across different species and the like?

DR. MENDRICK: Not yet. Certainly Paul Watkins and others have some of that work ongoing. We haven't done that yet, but again part of what will be interesting to see are the results from the *in silico* effort.

I'm certain that it's not just genetics. There are going to be other things that are going to play a role, such as the environment. Unfortunately there are too many things to do and we have to prioritize what we do with that.

PARTICIPANT: Donna, I had one question around the hepatotoxicity working group you formed. I think it's unique in

terms of how you're operating. So how does that group operate with respect to other proposal review processes, such as the whole proposal review process that Bill runs out of his office, and then the SAB Advisory Committee meetings as well.

DR. MENDRICK: Right now they're completely separate except that now Paul is beginning to overlap. We've been trying to get expertise from the group because they're unique. Clinically what do you need? Again, not just to identify that someone has dilly but how do you manage a patient? What kind of biomarkers or what kind of imaging do you need?

On the preclinical side, what is needed to identify some of these drugs and make better compound decisions going forward? I deliberately assembled an eclectic group so I'm not going to get a consensus on everything and that's fine, but we're trying to get feedback on the various projects.

We focused first on that large preclinical project because I didn't want to burn everybody out. We just had a meeting a few weeks ago where we updated everyone on all of the other projects we have going within the division, or at least most of them, on the various aspects of liver because they kept thinking that's the only thing we're doing. So, we brought them up to speed on all the other things we're doing.

We certainly hope we can get a lot of feedback from them, so right now they're not synced in but their information is certainly valuable and we are listening to them.

PARTICIPANT: And how often do you meet with them?

DR. MENDRICK: : We've been trying to not overwhelm them, so we've had two meetings, we've had a few phone calls and, in fact, some of the members are saying they'd love to have more calls so we're going to be bringing them in more.

I really didn't want people to get so frustrated that they disbanded because we were overwhelming them. It looks like we're edging toward actually getting more feedback from them as we go forward.

DR. HANIG: Just a quick question. How does your group interact with the PSTC hepatotoxicity working group, and also the group of people that John Senior interacts with at his yearly meetings?

DR. MENDRICK: Well John Senior is on this group, so he's a member of this working group. Federico Goodsaid, who has been very involved in the predictive safety testing consortium, is on this group. A number of us in this division listen in and participate, at some level, at a number of those working groups.

I'm more focused on the translational medicine working group with the predictive safety testing consortium. We've been

listening in on the liver. We've been listening in on the kidney. I'm involved in the cardiac hypertrophy working group.

So we're trying to keep our finger on the pulse of what other people are doing. We definitely don't want to repeat what other people are doing, and part of this issue of looking at what's needed in the clinic arose because some people felt that the predictive safety testing consortium group was so focused on the preclinical side that they were missing issues clinicians needed.

So, with that feedback, and once we start getting data on the multi-OMIC study, we will have to start bringing these groups in, as well as some of the people in Europe.

Agenda Item: Division of Personalized Nutrition and Medicine

DR. KAPUT: I'd like to welcome everyone to NCTR. We realize it's an extra burden to travel here and also to participate in a lot of the activities and review all these documents.

Our division is relatively new. It was formed three years ago by putting together biometry, which consists of mathematical statisticians, with the Epidemiology group because both of the directors had left.

Our mission is much like those of the others, which is to improve personal and public health. As the title of our

division goes, that’s exactly what we’re trying to do. We’ll make some comments about the concepts based on personalized nutrition and medicine because I think that’s what forms our approaches to developing projects.

We have analyses of nutrients, toxicants, lifestyles, and genetic factors that interact to contribute to health maintenance and disease risk. Our emphasis has been, at least in some of the human studies, on the development of obesity in children and adults.

I’d like to start with the biology we have to address, which is almost all of the data we’ve heard today and all of the recommendations we have for health, medicine and risk factors for exposure to toxins that essentially comes from population groups.

You take the average response of a control group and the average response of either a case like diabetes for drugs or for a genetic risk factor, and you calculate an average based on the population group.

You all know this but you probably don’t think about it on an everyday level. We are trying to address if that population risk factor is good for me or you in our division.

I would argue that because I have not been in a study in which my genetic analysis has been done, my lifestyle measured or my exposure to BPA or some other compound tested, I

don’t know whether the risk factor we know about is applicable to me or you.

If we’re going to do personalization and apply it to a human, we have to come up with a method to do the study since the way we currently do science is based on populations. What’s the path to knowledge?

The logic of the experiments we hear about, particularly from our geneticist friends, is that they are looking at some group, usually a European-based group, who say the study was underpowered because they had 500 people or 1,000 people in the study.

They want to get to 20,000 people and, in reality, there’s a new call in the U.S. to put 200,000 people into a GWA study. Now think about the logic based on what we’ve just said, which is the assumption that everybody in the study is going to go into the same genetic, cultural environment food bin—that all of their interactions are going to be the same. That’s what gives you the statistical power when you go from a small sample size to a large sample size.

We know, unequivocally, that every person in this room is genetically different. We can do the test today in the lab we’ve built and we can show you that you’re genetically different. If I were to ask you what you eat or what your exercise patterns are, or what you’ve been exposed to as you

came down here today, everyone is going to be slightly different—you'll respond differently.

This logic doesn't really work because what's happening in reality is that it's spreading the signal out and increasing the noise of the experiment.

Our view is that we have to start thinking about this in a different way, and as you go up into Dr. Slikker's office you'll see this little sign in one of his bookshelves. We know this now and yet we still continue to do the experiments the right way.

The reason we have this diversity, of course, is because we have nutritional diversity; we have different compositions of agrafoods, we have different food preparations, food culture and food processing that changes our exposure to nutrients. There are variable pathways to health and disease, and of course, we're genetically different.

So our division is trying to develop the experimental strategies that are going to look at how to develop personal risk factors. If you're going to do that, we believe you have to have genetic and genomic analyses of every individual or every cell you use— for every model system you have.

So we developed a genomic laboratory that doesn't quite overlap with Jim Fusco but, nonetheless, has all the tools. Now we have a nex-gen sequencer, the illumina bead

station, a RTPCR with an auto loader, and the old fashioned Sanger dideoxy, and we're tying that in with system, which I'll talk about briefly.

You need evidence-based data and a mechanism, and that's one of the reasons I'm happy to be at NCTR. Today you heard all the strengths of the other divisions on getting data through which you can understand the basic mechanisms of exposure or responses to various compounds.

As a scientific community we've been focusing on disease biomarkers, but what we're also interested in health biomarkers in the long run. How do we know if Jim is healthy so that he will not get a chronic disease later in life? Can we find some markers early in life that will predict what my outcome is later so I can take steps to intervene earlier rather than later? I have a lot of personal stories about that but we won't talk about them now.

We also need nutrient and physical activity assessments. One of the most unfortunate things about modern science is that it's soloed, as Don has said. So if you go to NCBI's databases and push on the database button, the whole page will fill up, and it will be all proteomic, metabolomic, genomic and transcriptomic tools. Not one spot on that website on the NCBI will have anything to say about your lifestyle or your nutrient assessments.

Yet if you pick up your iPhone you can have about 100 applications for physical activity and/or diet intakes. We don't have those tools. So we're working across the agencies as well as within the FDA to develop these tools.

We need to have our statistician friends in our division, so it's good that we have the biometry division. I thought it was a brilliant move to put the statisticians in the same group as personalized nutrition because we have to develop new algorithms to understand these individual risk factors. They're not here yet. Being able to develop that in our division is quite good.

I can't really talk about it because we haven't done much but if we do all this work what does it mean for society? How do we apply this to real life? We have a mission to try to do a cost benefit analysis for the implementation of our system.

I tend to show our structure of our division in this way. We have about 25 people. We're one of the smaller divisions. We have research statisticians here. We also have statisticians completely dedicated to the National Toxicology Program. Then, we have themes or areas of working in humans, stem cells, genomics, and in animal work with some metabolomics.

This is to show that we're working together as a team and, in fact, in one of our projects, almost everyone except three of the NTP statisticians participated in our Delta

project. I'm quite proud of that because they've all participated and helped.

It also shows my management style; I'm trying to have individual researchers, no matter their level, lead if they can and to develop their careers. That works for a lot of people. It doesn't work for some people, but that's a management choice I've made.

Our platform is to try to vertically integrate model systems. So, we have stem cell biology, models of how nutrients, toxicants and drugs affect adipogenesis, as an example.

We're developing the use of mouse embryonic stem cells for toxicology screening under Aimee and Deb Hansen. This is human adipocytes—adult, not embryonic. I want to make sure that's clear. We're working with CBER on this, CDER, and we've also visited the National Institute for Science and Technology.

Just last week I visited Y Cell and the Morgridge Institute up in Wisconsin, and they are also interested in working with us to develop a database for stem cells that's not available right now, as well as some aspects of standard operating procedures, which this field has none.

We have some laboratory animals, and even though that's really my background, we haven't focused on it too much because we've tried to get this up and running first, as well as our human studies. Our human studies are done in collaboration

with the Division of Systems Biology, the USDA, and then with Delta communities in the Delta region of Arkansas.

In addition, we have some exome sequencing, and I'll explain that in a minute through our vitamin project. These are just examples. The idea, of course, is if we do some work in stem cells or cell cultures then we could actually test them in laboratory animals, and then we could test them in humans.

Each model system has advantages and disadvantages. In stem cells you really can't look at exposure in an adult animal or in a neonatal animal, but you can do mechanisms. By doing the mechanisms in the laboratory animals we hope to form our human work.

Just as one example of our work, we have also used C-13 labeled glucose in an adipocyte stem cell model system. The idea was to look at the affect of fructose on the metabolism of glucose in the stem cell.

Let me just preface this by saying this is so controversial that we thought we would have to do some pilot experiments in order to show that it was worth doing. So this is essentially pilot data.

So, we had C-13 labeled glucose only at the first two carbon positions, and then we had cultures, which had a control glucose at five millimolar. Then, one culture had ten millimolar of fructose and the second culture had twenty millimolar of

fructose, and then we had ten millimolar glucose and twenty millimolar glucose.

You ask the question not where the fructose goes, not where their carbon goes, but what does fructose do to the pathway of glucose metabolism. Down here you'll see that the fructose actually decreased the amount of label in lactate, and it's a little bit off the bottom so you can hardly see.

Every measure that we had, every set of metabolites involved in central metabolism shifted—the fructose shifted to increase NADPH production, glycerol production, and triglyceride palmitate. In this model adipocyte, fructose changes glucose into fat, and this fits with the data that comes from the liver, as well as some other tissues.

We have to follow up on this and do a larger study in order to prove this point. I think it directly addresses this question about obesity in the American population because, as you know, high fructose corn syrup is virtually in almost every manufactured product that we have. Now the food companies are, in fact, removing this due to pressure from consumers but it is still a significant problem in the U.S., as well as around the world.

This work is being done with a company called SiDMAP, stable isotope mapping, who are experts in this. Rick Beger is in the Division of Systems Biology as our close colleague and

has been helping us, and he will be able to do this analysis on his systems. He can do it now so we are going to be shifting all of our work from the metabolomic work from SiDMAP into Rick's.

The second project that we have is one in which we look at better nutrition in children in a summer day camp in the Delta region of Arkansas. This county is Phillips County and it's the poorest county in Arkansas, which means it's about the poorest in the United States. The average life expectancy of people who live in that county is 70 years.

People who live near Fayetteville and Bentonville up in the northwest corner of our state have an average life expectancy of 80. There is a 10 year health disparity there.

In collaboration with the USDA, we go to the summer day-camp and we measure the vitamin levels in kids at the beginning of the day-camp that is five weeks long, when the day-camp ends, and then one month after they go home. We should see changes in metabolites based on the food intake they have. We feed them a better, nutritionally-balanced breakfast, lunch, and two snacks.

We're doing this to see how each individual responds to the better food and, although, it falls out of our experiment and we get a lot of good data for it, but also what the levels of serum vitamins are.

We do a genetic analysis of each child, and here's just the SNPs. This set of SNPs we're looking at were highly selected by *in silico* data mining. They are a gene involved in micronutrient metabolism that map to quantitative trait genetic myocytes involved in a chronic disease of obesity and diabetes that also have a coding snip, so it changes the protein coding sequence.

We're using this only as a model, a pilot set to show how you do data analysis with complex data sets. We looked at the snips and you can see that the kids and adults, we don't know who is who, can cluster into various patterns. This is a hierarchical clustering of the snips in the individuals.

We also look at the metabolite levels. You can see there's a cluster of individuals here, but then there are several that are spread throughout the rest of this principal component analysis based on 11 metabolites, 9 of which are measured in Rick Beger's lab and two in our lab.

Here's what we're trying to do with this data. Why are these individuals different from the cluster here? So this individual falls into this cluster, this individual falls into this cluster, this individual falls into this cluster.

As an example, you can ask the question of why does the individual who's falling into this genetic cluster differ from the individual right next door? This individual is in the

same cluster—very similar, but doesn't appear next to this metabolite level.

We went back to the genes that are different or the snips that are different between these two individuals, and found four that are. Two of them are involved in niacin metabolism and one is involved in methionine metabolism. The one off the chart is in vitamin E.

Here's what we're trying to do. We're trying to link your food intake, your metabolite levels, and your genetics in one individual and ask the question of how can we explain why a metabolite pattern is as it is?

We don't have the nutrient intake analysis on here. We don't have the activity levels we also measured on here— we put little body bugs on the kids and we can measure how active they were with an accelerometer.

The concept we're working on here is to develop a research strategy to look at individual risk factors. We believe that when we do, we will be able to cluster people into metabolic groups. I will have more to say about that in a minute. That's just one of the concepts that we're working on.

In addition, we have a lot of work in the biometry division, which is looking at mathematical models or developing algorithms to analyze such high dimensional data sets. This team is led by Jim Chen, who has been a stalwart at NCTR and FDA as a

statistician for over 25 years. He's looking at molecular capacitation algorithms for disease diagnostics, prognostics, treatment responses for a patient's assignments, and methods for gene set enrichment, and then for rapid threat assessment.

For pathogens, we're trying to develop a better classification algorithm for salmonella with CDC. That is causing us to think about databases because the databases are not well developed, so I'm getting this up very rapidly

The SAB recommended that we recruit more statisticians. Right now, we've only replaced and we have to do better work at that. We want to have increased collaboration with the FDA so a statistics workshop is being planned. We had a stem cell workshop at UAMS, in which we had FDA representation from CBER.

We have the food safety database. We found a very good partner in the Virginia Bioinformatics Institute, which has a $27 million grant in developing a pathogen database. We believe that the agency should have a research database that connects with these guys because they have the resources to help the FDA do its work. We're discussing that with them, and we had a workshop here in this room and telephone contact with people at CFSAN and Vet Met in food safety analysis with the algorithms.

Of course, they wanted us to develop an NTP historical control database. We would love to do that. We don't have the personnel, but we believe that's an NTP initiative.

There are other recommendations that I've handed out so I won't go through them. This is the stem cell workshop. We visited CBER. We visited NISS and, as I said, we went to Wisconsin and the Morgridge Institute at Wisconsin.

We're developing database of WikiLIMS in order to manage sample flow. Rick Beger is taking the lead on that for us and we're helping him develop that. It will help DPNM. We're also talking with CBER about how we can make sure the system for stem cells works for them. We're developing a nutritional phenotype database with some Europeans.

We needed expertise for nutritional exercise. We have a visitor from Brazil for the year that has showed us that we actually do need this type of person in our division. I have some global connections. I've been asked to participate in the EU framework project; it's a fun project. It's personalized nutrition.

A new one on the technology for the effects of nutrients on health is being written. I will try to be on that one. This one just came through the door and it's not likely that I will have time to do that.

We have other initiatives that we've been asked to do with New Zealand, with the Dutch Nutrigenomics Consortium to review it, and I've just been asked to be on the executive committee of the nutrigenomics organization. I'm the first international member on that.

We're making connections inside the FDA, but it's my strong feeling that in order to do gene nutrient interactions for either health or medicine, we have to think globally and we have to interact because of our genetic profile—if everyone in this room is too limited to give us a full understanding of all those interactions.

I will just back up and say this group here, which is Irish-led, has already produced two manuscripts that have been submitted for publication, and I heard the data in which they did challenge experiments looking at individual responses to health in the international meetings.

We're trying to play catch up even though we've had these concepts for a while. We need to stay with this type of program because the EU has gotten at least this one program funded. This one is highly likely, given the people that are on it, to get funded.

Both of those programs are looking at personalized nutrition. They have comparable programs in personalized medicine. They're developing new strategies. The FDA is going to

be regulating these types of activities and I think we have to have that type of research within.

When Bill hired me several years ago, he said think three to five years out. Well it's here. We're not talking about directive-to-consumer genetic testing, and yet we don't know the whole spectrum of human genetic variation.

We have to be doing these experiments. We have to be working internationally in order to do that. Our view is that these are the applications for just the general public. We think we cover most of them for the major areas. For the FDA we are working to improve personal and public health risk assessments.

In my opinion, the approaches I just briefly talked about might be wrong, but we need innovative science that challenges the way we do these experiments so that's what we're trying to do here. Sorry for going a little long Peggy, but I think you're trying to have me catch up for all the other people.

DR. HINES: Nice presentation, but one question— when you say genomics, are you including the epigenome?

DR. KAPUT: We had not yet but, of course, the platform that we have is the Illumina B, which can do methylation. We will do it. There's no question.

DR. HINES: And beyond methylation, microRNA and histone modification, which, I think, is going to be even more crucial.

DR. KAPUT: As you heard we have to pick and choose, so we have a priority list, which is genetic variation, methylation, and then the microRNAs. We do have a project in microRNAs for the stem cells. We're interested in it, so it's just a matter of how many hands we have essentially.

DR. BAKER: Nice presentation. You're going beyond genetics and looking at OMICs and things like that. We know that OMICs change with age, they change with gender, and they change with diet. This is well understood. If you're talking about personalized medicine we really need to understand how these things change with time.

It's not often, or could be it's not your snapshot at the present time, that will define how you're going to respond. How you got to where you are today could depend on that trajectory. Are you addressing this temporal aspect?

DR. KAPUT: I didn't have that slide but we look at individuals over time. Right now, they are short times because the strategies we've developed are controversial, but we think we have to develop them to show pilot data on a smaller snapshot than a year, so some projects are six months.

For the children in Arkansas, some of them come back to the day-camp so we'll have them the over years to start looking long term. But we first have to show which data sets are needed to put it together and then we can start doing those experiments. You're absolutely right, it will change.

DR. HINES: That's a very good question. Are you taking advantage of some of the PK/PD modeling software out there that looks at, for example, changes in pharmacokinetics as a function of age?

DR. KAPUT: Not yet, but it's a good suggestion. It's just a matter of how many people we have to get the work done.

DR. HINES: But those are available—SIFT, popgen, things like that.

DR. KAPUT: I agree, and we should be looking at them.

DR. HANIG: In terms of personal medicine and drugs what are you doing about the aging population, and let's say predisposing conditions of disease of one sort or another? Typically an awful lot of drugs that are approved go into an aging population for the rest of their lives, and yet this has not been the paradigm for testing.

DR. KAPUT: We are not doing anything yet with an elderly population. Our focus has been on young—model systems in animals or stem cells to do basic mechanisms; however, our real

emphasis is to do children and mothers first, quite frankly, because if you don't get the right nutrients *in utero* and in early childhood, you're going to have those problems and you're going to need the drugs.

Regardless of whether the FDA should be in prevention or not we think these basic mechanisms of understanding how to promote an individual's health are critical for the agency. Our view is that we've got to start there to get the basic knowledge of micronutrient intakes, et cetera, worked out, and then I would be happy to do that if you can give me some money to do it.

DR. HINES: That's a deal.

Agenda Item: Division of Genetic and Molecular Toxicology

PARTICIPANT: As Bill said a little bit earlier today, we've had a name change in our division, too. We're now the Division of Genetic and Molecular Toxicology, not the Division of Genetic and Reproductive Toxicology. Bill explained the reasons for that so I'm not going to repeat those.

We have two really main focuses in the division. One is to provide the agency with expertise in the current, reviewed genetic toxicology assays. The other is to develop new methods, tools, approaches, assays and new things that might be needed in the regulatory context.

For those of you who are really not familiar, I want to give you just a little bit of a background on how genetic toxicology data is used in the agency. It's primarily used for hazard identification, although there are some applications that actually get it more into risk assessment.

The hazard ID issues include the preclinical safety evaluation, this would be for CDER, food additives and contaminants, this would be for CFSAN, and food contact substances. Veterinary drugs are handled in CVM in a very similar way to human drugs handled in CDER.

I've listed these dietary supplements because they're reflective of the types of chemicals where decisions are made or not made based on a, generally, very small amount of information. When you have a small amount of chemical information, often what you have is gene-toxicology information.

Some of you will recognize this diagram from the critical path document. I want to show where genetic toxicology fits in the drug development and approval process. This is a little pipeline here.

The major use, at this point, for genetic toxicology is in preclinical safety evaluation, and it really is hazard identification. I've got a little arrow here, showing that we're trying to make some progress into developing biomarkers in new approaches that ultimately could be used more as you move into

clinical development, and actually, even in some of the human clinical studies but that's still just a little arrow at this point.

In the division we have 26 government positions. As of yesterday we have two commissioner fellows, one individual just joined us yesterday. We have seven ORISE post-docs. I wanted to emphasize that because of the new focus on international activities, 2 of these post-docs came directly from China to work with us, and another came directly from Pakistan to work with us.

We also, at this point, have one visitor for, I believe, 6 months. She came specifically to our group because she wanted to learn one of our assays, so we do a lot of training. This year we had 3 summer students.

We divide our research into 4 themes, the first one being the current regulatory assays. We do a number of different activities. We have a heavy focus on providing advice and expertise, and we work with various types of documents.

ICH is human pharmaceuticals and veterinary drugs. The ISO documents are probably used in a number of places in the agency, but I know for certain that they're used in devices. The red book is a CFSAN document, and most of you are probably familiar with OECD. I underlined OECD because there is going to be a lot more activity coming up in the next few years so

they're revisiting some of the gene-tox documents at this point, Several of us are going to be representing the agency at these meetings and working on these revisions.

We do provide consults for the FDA reviewers. Some of us are members of the gene-tox network, which cuts across the centers. We also participate with CDER, the Center for Drugs, which has a specific gene-tox committee and that's where we often get consults for reviewing data, particularly data that comes in that reviewers have questions about.

We also provide a lot of interaction and consultations in the international regulatory community. We do a fair amount of targeted research using these regulatory assays. I'm not going to really spend any time on that because I don't have too much time to spend on any one area.

In addition, we're just starting to address the question: Are these current standard assays appropriate for nanomaterials? I know Paul is going to talk a little bit more about our nano research and our nanocore facility when he speaks. I believe that's this afternoon.

Our second theme is what we call chemical specific research. Often we will be involved—Fred did a really nice overview of the NTP studies that we do, and our group often does some of the mode of action studies that are planned in conjunction with Fred's group.

Right now, some of the things we're working on—aloe vera, which Fred also mentioned. Our colleague in CFSAN had a little bit more information on the aloe vera and, in particular, wanted to know whether the aloe vera was mutagenic— that is, the samples that were used for the cancer assays.

The same colleague has interest in methyl eugenol, which is apparently a carcinogen, but we don't know what the mode of action is so we're trying to figure that out—this has actually proven to be somewhat difficult. We thought it would be rather straightforward, but so far we haven't been very successful in figuring out if it might have a mutagenic mode of action.

Furan is an NTP chemical and we're, again, working with Fred's group on that. We thought that would probably be a mutagenic chemical that would be relatively straightforward to deal with and that's also turning out to be kind of challenging.

TEMPO is—I'm not sure that the correct word is contaminant—in drug products. So, one of our colleagues in CDER wanted us to take a look at TEMPO for its ability to be mutagenic.

We've also just finished up a series of cigarette smoke condensates that we've looked at for comparative mutagenicity in collaboration with CDC through an interagency agreement.

Our third theme is the promise of new methods and approaches. We’ve been particularly pleased with this first project, which is the development of a new assay using the PIG-A gene to look at a mutation, and I’m actually going to tell you just a little bit about that. I don’t have too much time to talk in any detail about the other assays but I want to highlight that one.

The project on using microRNA expression to identify carcinogens: the idea here is that maybe carcinogens will have a different microRNA expression pattern than chemicals that are not carcinogens. If that is the case then that would give us a better way to screen for chemicals that might be carcinogens before you actually do the cancer bioassays. And that becomes important in a number of different regulatory situations, especially for the preclinical safety evaluation.

We have a large program looking at specific cancer mutations. That program is standing and this is headed by Barbara Parsons and Page McKinzie.

We’re bringing an assay that’s been used primarily in Japan on board. It’s called a gpt delta transgenic mutation model. It has a construct that’s inserted into the animals, and it has the capability to identify both point mutations and some small deletions, so it gives us a little more power, if you

will, and slightly more ability to pick up chemicals that are mutagens.

Our fourth theme is really a broad, crosscutting area of research to improve risk assessments. In FDA, we don't do a lot of quantitative cancer risk assessments in particular, but there are some that are done, and that's actually quite important. In the scientific community there's a lot of discussion and a lot of improvements on how cancer risk assessment is done so we're involved with that.

The rodent to human extrapolation issue—at this point we're primarily focused on Barbara's program with the cancer biomarkers where we can get both human samples and also rodent samples. That gives us some ability to do some comparisons.

In the last year or so, there has been a revolution in the gene-toxicology community. There is increasing evidence that there may be actual thresholds for chemicals that are mutagens, and if not actually thresholds, at least indication that the dose-response curve is quite non-linear. That becomes extremely important when you start talking about your models for doing your quantitative risk assessment.

Another area is looking at improving ways of looking at mode of action for chemicals that are mutagens and carcinogens and, again, this plays into risk assessment.

I want to spend just a minute here to tell you about the PIG-A gene mutation assay and how it works. It's actually pretty simple, easy, and appears to be working quite well at this point. Basically, things that are good about it are that we use a mutation that actually happens to be—or use a gene—on the X chromosome, which means that it's readily available to use in various species, such as rats. At this point we've done rats, mice, monkeys, and humans. That gives you lots of capability potential for interspecies work.

The way the assay works is that this gene codes for an enzyme that gives GPI anchors, which if you can see up here in this normal cell, we've got these GPI anchors and these anchors tether surface proteins that you can see up there. Because you have these proteins you can use fluorescent dyes and it allows you to identify those cells that are normal.

The mutants, on the other hand, are missing these GPI anchors and, consequently, they don't have anything on their surface to bind to our fluorescent dyes, and so they are going to look different than the mutants. The way you do the analysis is basically by putting the cells through a flow cytometer. This allows you to score lots of cells in a relatively short period of time. It's really a very promising assay.

I want to emphasize that we have a number of external collaborations. I'm not going to belabor this because I think I

might be running a little slow here. We work with industry, other government agencies, other regulatory agencies, and also nonprofits. We do have an emphasis on multidisciplinary teams, which has already been mentioned by some of the other divisions. It really is the way we need to do research in this day and age.

I'm going to move to a series of slides that dealt with specific recommendations that were made by the site visit, and I'm going to move fairly quickly through these.

The first one—there was the suggestion that we might need more staff for our nanonmaterials research. Again, this is assessing whether or not the current standard gene-tox assays are appropriate for assessing nanomaterials. We have added an additional support scientist to the group.

I did want to emphasize that we're planning to utilize several different assays, and the way we will do that is assign the individuals in the division who are already familiar with these assays to do the nanomaterials work.

Also, we expect to, and we really are already starting, to collaborate extensively with the people that are in the nanocore facility, which Paul Howard is going to tell you more about when he gives his presentation.

For the PIG-A assay, the recommendation was that we take a leadership role in moving this assay forward to being in full use. There is an international collaborative trial that is

going on. One of the interesting things about this assay is because so many people have gotten excited about it, there are many different groups who have already started to work with it.

We really don't know all of the appropriate parameters, so it's kind of like we're moving faster than the science really allows us to. One of the things we're really focusing on in our group is making sure we're looking at various approaches and parameters that are different than those being used in the standardized trial.

For the microRNA project, again, this is using microRNA expression to see if we can identify chemicals that are carcinogens and non-carcinogens. Tao Chen is the lead on this and he's actively participating in a collaborative, multi-lab project that's going on. In fact, the meeting is being held in Washington right now so he's actually in Washington at that meeting.

For the cancer biomarkers program, the suggestion was that we really needed to expand our external collaborations. We have a CRADA that's in process and we hope it's actually going to be approved this week. As I understand it, it's being reviewed this week. It basically deals with mode of action for ethylene oxide. We'll use the cancer biomarkers and our standard transgenic assay mutation markers, and do some comparison with those two approaches.

One of the things that Barbara and the other people of their group are doing is looking for opportunities to utilize tissues that have been generated in other studies. There are people in our group that have done this over the years; we've had some *in vivo* studies and some on the gene mutation from the transgenic animals. Barbara's group then went back and looked at the specific oncogene tumor suppressor gene mutations that are occurring in those tissues. It gives us a lot of ability to do comparisons.

The recommendation that we continue and expand interactions with regulatory centers: I just mentioned that I'm, in fact, on nanomaterials— one of the two members of the FDA nano task force. Paul Howard is the other one.

I've already mentioned the chemicals we're looking at. These chemicals have been requested by our various regulatory colleagues. They said, "you know we'd like to know something about this chemical, and can you do that?" So that's what we've done.

We've participated actively in the STEP program, which I don't believe has been mentioned. It's a program Peggy manages, that allows for training people in other centers. We're looking forward to opportunities to collaborate with the Center for Tobacco Products and also with CDC.

Moving into epigenetics, I'll just mention quickly we have two collaborations with Igor Pogribny, who is in DBT. So we are doing that, and more high-risk, big payoff projects where we're going to try to utilize a different marker, which would be an autosomal marker for PIG-A assay.

For *in silico* databases, we're doing a reevaluation of the NTP mouse lymphoma database to align it to current standards to get a database that can be used.

DR. AFSHARI: Martha, I'll ask one question. In the area of new technologies and risk assessments there's certainly a lot of merging in what the cancer bioassay should look like moving forward. Can you give us a sense of how your group is positioned within that discussion in the agency?

DR. MOORE: I guess I'd characterize us as being more in the up front part of that process. By that I mean the development of cancer where you have the exposure on one end and then a bunch of things happen before you actually get tumors.

The work our division would focus on would be the first part of that process. So we would be looking at mode of action for a mutation if, in fact, the etiology of that tumor is through a mutational event, and trying to understand how you identify whether you do have a mutagenic carcinogen or not.

There are several layers of issues here, so that would play into the overall big picture. We don't really have the

cancer expertise in our division. That would be, for here at NCTR, in Fred's division. We do work together. We're kind of going after the question from both ends where Fred's division is doing the cancer and we're looking at the earlier events, the earlier key events and tracking it as it moves into cancer. Is that your question?

DR. AFSHARI: Yes. I just wanted to clarify. I think it's good for the board to note, too. So the scope of action of non-genotoxic carcinogens' mode of action is outside of the scope of your division?

DR. MOORE: Well, basically, and I say that with some reservation, because if you do a good job of a mode of action assessment, and in large projects where we would do a good design for mode of action, you're going to need to look at the non-mutagenic possibilities at the same time. So we would get that information, but for the most part, we would probably be collaborating with somebody else.

This ethylene oxide project we hope to get approved through this CRADA has a number of collaborators in it where they would be doing some other endpoints, and we would be doing the big blue transgenic mutation model and the cancer biomarkers work that Barbara does. Then we'd put all of these pieces together.

DR. HANIG: I was wondering if you could tell us just a little more about TEMPO, what it is in structure and what the context is for the research?

DR. MOORE: Well, I'm afraid I can't tell you what the structure is. I'm not much of a chemist, but I can go look up some of the details.

The issue is that it appears to be a mutagenic compound. There was some evidence that it was positive in the Ames test, so my understanding is that this particular chemical and chemicals that are structurally similar can appear in a number of different drug products.

DR. HANIG: As an impurity?

DR. MOORE: As an impurity. I think I said contaminant, but maybe impurity is the more proper term. But basically, it's a by-product of making the drug. So the question becomes, if it is mutagenic, how much of it should you allow or can you allow in the final drug product? That's sort of the crux of the issue.

DR. HANIG: The other question I had was how much do you rely on the Comet Assay and what are your thoughts on it at this point?

DR. MOORE: Well, I guess I should preface my comments by saying I am biased. I've personally never been a particular fan of the Comet Assay. It is becoming more widely used,

particularly with the revisions of the ICH document, which has not yet been signed.

It's been pretty widely used in Europe so there's a lot of data out there. What we're trying to do at this point is get a good handle on the current issues. What are the various parameters that are important because there is going to be a guidance document written? It may not be written in the next year or so, but Japan has the lead for writing an OECD guideline for doing the Comet Assay.

Our focus here is to try to get enough information to have a key role in that. I guess that's a long way of saying that I think the jury is still slightly out as to whether the Comet is totally ready for primetime, and I think some of my colleagues would say it a little more strongly than I am, and in a slightly more negative tone as well.

DR. HANIG: Thanks.

DR. MOORE: Okay. Thank you Martha. I think we need to move on with the next part of our program, which is an update on various cross-functional activities. First, we'll have an update on the Office of Science Coordination.

Agenda Item: Update on Activities

Agenda Item: Office of Scientific Coordination

DR HOWARD: I still don't understand what the name means but hopefully I can at least explain what we do. Joe, in answer to

your question about TEMPO, TEMPO is a nitroxyl compound, which is used a lot for radical scavenging. If you generate free radicals in solution, you can use TEMPO to capture the radicals. It forms a stable radical adduct, and that's used by EPR to pick up radical reactions in biological samples.

It's used to control radical reactions in the synthesis of drugs where you either want to sequester them out or maintain a certain flow of radicals. The Office of Antiviral Products came to me about this problem. They came to Martha first, and it will be turned into an NTP nomination.

So as I'm going through this process, we are working with CDER to put together a more complete toxicological profile on TEMPO.

The mission of the Office of Scientific Coordination is really four-fold. The primary mission is to monitor and facilitate the interagency agreement between the National Toxicology Program and NCTR of FDA. By being the director of that office, I'm also the project officer on the FDA side.

Secondly, we want to be the principal FDA liaison to the National Toxicology Program. I was at the NTP yesterday going over plans for future activities.

Thirdly, we aim to conduct some toxicological studies. Dr. Beland described the studies that are being conducted in the division about chemical toxicology, but there are a few other

studies that don't require laboratory support. So we pick up some of the excess studies in this office.

Fourthly, it's the home for the nanotechnology core facility. I'll go through each one of these fairly quickly.

This is the structure of the office. I'm the director. We have the support for the National Toxicology Program efforts and support for nanotechnology. Two of the key people are Connie Weis, who is the program manager of the day-to-day operation and day-to-day interaction with the National Toxicology Program, and then Angela Corlett who is the budget analyst.

We added Robin Stingley about a year and a half ago to help us write the nominations for the agency into the NTP, and with her and a technical writer who's being hired, they will formulate the technical reports that are then published by the NTP.

Julian Leakey is a research scientist who is conducting some of the studies. Sandy Matheson and Sherry Lewis are scientists who support a lot of the projects. Sandy is going to be heading up a couple projects I'll mention, and Richie Furers handles the human risk assessment— our interaction with the FDA's risk assessment committee.

On the nanotechnology side, we have hired several people. Yvonne Jones is an electron microscope technician. She has 30 years of experience. We stole her from another government

agency. Yongbin Zhang is a research scientist doing nanotoxicology studies. That’s how the office is split, and you have handouts coming around for your reference.

The mission of the National Toxicology Program is pretty broad. It’s to support the toxicology data needs of U.S. federal agencies. It has both a science oversight committee, which is a board of scientific counselors that I know some of you have been on, but also a policy oversight committee with heads of all of the federal agencies that have anything to do with health. The director is the director of NIEHS, which is Linda Birnbaum.

NCTR and the FDA, NIHS, and NIEHS are the three organizations that form the NTP and helped it start in 1978. But the mission is to evaluate agents of public health concern through the development and application of tools of modern toxicology and molecular biology.

Everyone knows of the NTP for the two year bioassay. They cleaned it up and set a gold standard of how it should be done, but it’s much more than that. I don’t have time to go into it but it’s revising, for instance, reproductive toxicology studies. It’s coming up with new biomarkers of cancer development and disease development.

It maintains an objective, science-based approach to toxicology and it uses the best one, but also develops new

methodologies because with new tools available to scientists, it affects how toxicology should be conducted.

The interagency agreement between the NCTR and FDA came because it was obvious there was an overlap between things the NTP was studying and things the FDA regulates. An agreement was signed in 1992 because there are compounds that are regulated by the FDA that the NTP is going to study, but those studies will be conducted at NCTR. This is the 18th year of this interagency agreement, so it's been quite a successful program.

Again, we conduct on the interagency agreement, and here, at NCTR, we conduct studies on FDA-regulated compounds. The interagency agreement will also ensure that the design and conduct of the studies are consistent with the needs and goals of the FDA, meeting GLP requirements, but also meeting any of the goals of the NTP.

For instance, we've evaluated and established how to conduct total electronic pathology reviews of study slides, which normally required all the pathologists to come together to review the glass slides. With the NTP, we've established how to do that completely electronically, which saves on travel and the problems it generates.

The office provides oversight to ensure the studies are conducted in the most rigorous manner, but basically we just coordinate. I don't oversee the studies done in Fred's division.

He does, but I just make sure he has the tools to do what he needs to do.

Also, through this interagency agreement, we ensure that the data from the studies are available to regulatory agencies, U.S. and worldwide, to make science-based safety assessments. The studies on acrylamide have already been used by the European Regulatory Authorities to start understanding the risks from acrylamide. This is the outcome of this program.

As far as the organization, once an NTP nomination in the program is approved and it's of an FDA-interested chemical, an NTCR principal investigator is assigned or requested. I don't know how we state that, but they're usually in Fred Beland's division because that's where the cancer bioassays are conducted.

There's an oversight committee that has a long name—Toxicology Study Selection and Review Committee. Basically, this committee meets twice a year—May here and November at the White Oak facilities. Several of you around the room have been very involved in this, but the idea is to get the NTP scientists, the NCTR study scientists, the FDA center scientists both from regulation and a scientific level, and subject matter experts together twice a year to review the progress of the study so they can help make the right dose selection and help add biomarkers needed in the study.

It’s a good process the NTP is in favor of because the folks that are going to have to make the regulation at the end are very involved in the design and execution of the study, and I think you can see the advantages of that. The final products are scientific publications, NCTR final reports that are the QA-GLP report and NTP technical reports.

Two NTP technical reports that were just printed. One of them is on toxicity and carcinogenicity studies on androstenedione. That is going to affect the FDA because androstenedione is a drug of abuse. The other one is a study that was conducted here at NCTR. It’s the toxicity and carcarcinogenicity studies on ethinyl estradiol. This is the endocrine disruptor program, which was conducted in Dr. Beland’s group.

The reports have the pathology data tables in it and the cancer tables. These can be used by risk assessors to evaluate the risk of these products. This is a very powerful public health outcome to a product we have. When I say “we” I mean the scientists that conduct the studies.

Compounds that have been studied— I don’t know if these have been mentioned, are endocrine active agents, dietary supplements, food contaminants and food safety, pediatric

translational drugs, drugs and devices, AIDS therapeutics, photoactive compounds, and nanoscale materials.

You probably have heard from Dr. Beland about the studies on Bisphenol-A and diethylhexyl phthalate, which are plasticizers that are real issues.

Dietary supplements in Dr. Beland's group are studying aloe vera, but studies on usnic acid and usnea lichen, which is a lichen product people use to make tea, are also underway. If it grows, it must make a nice tea, such as bitter orange, which was a replacement for ephedra.

Glucosamine chondroitin sulfate which, other than vitamins, is the most purchased dietary supplement worldwide. As I get older I start to understand why, as well as butterbur.

Other studies, I know Dr. Beland mentioned from his division, are studies on acrylamide, furan, and melamine and cyanuric acid. These are current studies.

Pediatric—ketamine and other pediatric anesthetic agents are going to be discussed a lot with the neuro review. The animal studies on cellular telephone radiation are being conducted by the NTP in Chicago and we're doing mechanistic studies and *in vitro* studies here, as well as analyzing some of the tissue. I'm sure Dr. Beland mentioned the work on triclosan, which is very important to the EPA as well as FDA.

Studies on AIDS therapeutics are completed and the reports are being written on combination therapeutics, both for the chronic study that Dr. Beland's group did, and also for the genetically modified mice, which Julian Leakey and the Office of Scientific Coordination conducted. There's a current study on goldenseal berberine, which is being conducted in Dr. Beland's division.

In nanoscale materials, there's a large effort on nanosilver out here, both in Dr. Beland's division and in the neurotoxicology division, as well as in concert with the Office of Regulatory Affairs here looking at methods to detect and analyze nanosilver.

For instance, the Environmental Protection Agency has approved nanosilver to be used as a microbicide in agricultural products. Just imagine what that's going to do to the FDA when the tsunami of nanosilver-treated strawberries, plums, blueberries, et cetera come through when they're using that to try to kill E. coli.

We're working in concert with the nanotechnology core and ORA to try to develop the technology so when the centers start asking for an analysis of nanosilver on strawberries, et cetera, or the field labs have to go sample strawberries and detect nanosilver, the methodology is here. This will be the focus for ORA for nanomaterials.

Also, there have been studies conducted both in Dr. Beland's division and also in the Office on Oxides of titanium and zinc, and also nanogold.

The interagency is impacting public health by providing both hazard identification and dose-response data. This report is essentially all you need to know to do risk assessment—well not all, but it's a huge amount of data for risk assessment. -.

Dr. Beland conducted studies on urethane and ethanol (? while the studies were ongoing and as results were coming in, the distillers of hard liquor changed the distillation process to reduce the urethane level, which is a public health impact.

And then there are ongoing studies on Bisphenol-A and furan, which I'm sure Dr. Beland mentioned. The public health impact is going to be huge.

That's the interagency agreement with the National Toxicology Program. Looking at the capacity in the office to conduct toxicology studies, Dr. Julian Leakey has done work on work on acute and sub-chronic studies with glucosamine chondroitin sulfate, and he's also conducted the studies with usnic acid.

Dr. Sandy Matheson is going to follow this up with a chronic study on glucosamine. People are consuming this for long

periods of time and we don’t really have any chronic bioassay results.

Also, in collaboration with the National Cancer Institute’s nanotechnology characterization lab between the office and the Division of Neurotoxicology, we’re going to be doing some studies in 9 human primates with drugs that are moving into the clinical phase. We have a Memorandum of Understanding with them to conduct these studies. Yongbin Zhang is going to be conducting studies on nanogold and nanozinc-oxide.

Again, these studies are primarily not requiring a lot of laboratory support except for Yongbin’s studies, which is primarily *in vitro* work. That’s why they are in this office.

The purpose of the core facility is to serve the nanotechnology needs of NCTR, the Office of Regulatory Affairs, the other FDA centers, and other U.S. government institutions such as the National Toxicology Program.

Nigel Walker, the NTP Project Officer for our interagency agreement, and I are working together to utilize this facility to support NTP studies. You can see how it’s playing a role. It’s not only supporting NCTR and ORA efforts, but also toxicology studies that will move into risk assessment studies on FDA-regulated products.

Nanotechnology boils down to equipment and expertise. We have received funding from FDA from Dr. Slikker and the allocation he gets from the Office of Regulatory Affairs, from NIH last year who provided us with a considerable amount of their FY10 eRA funds, and we're also receiving support from the National Toxicology Program itself for this core facility. I'm going to just touch on the people, equipment and projects.

We have an NCTR side and an ORA side for the nanocore itself. It's interlaced but from a management point of view there is a line here. We recruited an EM director. We're recruiting and we have three excellent candidates who are managing electron microscope nanocores at other facilities. So, we have excellent candidates coming in.

We have a senior EM tech, and we have an advertisement out for another EM tech and a nanotoxicologist so we have understanding, in-house, on the behavior of these materials *in vitro.* We also have a spectroscopist and two lab chemists to operate the equipment that will be used by NCTR or ORA in the rest of the FDA facilities.

Dr. Beland has allowed us to use Barbara Miller, who is a chemist in the Division of Biochem Tox. She's on loan to nanocore, providing tremendous expertise in particle size analysis. We're always very thankful for her work with us on that.

On the ORA side, Office of Regulatory Affairs, they don't have a director but Sean Linder has been serving in that capacity, working closely with me on establishment of the core. An FDA commissioner's fellow, who came from Brookhaven National Labs, was trained there on nanomaterials—excellent scientist I hope we get to keep. And then the FY11 and FY12 budgets have positions.

There is a tsunami of nanomaterials coming through the agency. It's at CDER, CBER, CFSAN, and others right now, but it is going to hit ORA like a ton of bricks a few years down the road when they have to go and look at in the marketplace whether these products are there or not.

This is getting ORA ready with the expertise, knowledge and experience to be able to handle that when it comes in—when CFSAN says, "what about nanosilver migration out of this food wrap material," the expertise will be here to really assist and go look at that.

As far as equipment, I'll just go quickly. You have this in a handout, but we have a 200 kV transmission electron microscope. It was calibrated on assessing the difference between nanogold atoms. We also have a scanning electron microscope, which has tremendous capacity, and we'll be purchasing a new TEM.

As far as elemental analysis is concerned, we have two ICP mass specs to conduct elemental analysis because most nanomaterials have unique elements within them. This is just going to be a dynamic piece of equipment where we're combining the power of HPLC to separate nanomaterials with ICP mass spec to detect them. It has an in-spray nebulizer to directly do a metals analysis. This is what will be used to really determine the speciation of silver in products. TEM, SEMs, and also x-ray fluorescents will be used.

Again, the microscopy is the EMs dark field and bright field microscopes, which are key for working in tissues and nanomaterials. Confocal Raman FTIRs, so it's the power of confocal microscopy with Raman detection and FTIR detection to pick up nanonmaterials based on a unique Raman signal, and you have to have an atomic force microscope for that.

Classical flourescence infrared confocal equipment. But you really need to know what you're applying to your cells. Let's say Syed Ali is going to put nanocell cells in culture. If you use one piece of equipment, you're in trouble because all these pieces of equipment are based on theories and have imperfections in their theory, or error in their theory. So we have multiple pieces of equipment to determine the size of particles.

For instance, if you take liposomes and try to determine their average size using dynamic light scatter, you're going to be off anywhere from a minus 50 percent to a plus 100 percent, and we found this out last week. However, if we use a different type of technology called visual particle tracking where we're actually tracking the movement of these particles in solution and, based on theory, calculating their size, it's dead on accurate. Each of these has its own limitations. We need multiple technologies to understand average particle size.

Space has been allocated to us in the ORA building. I'm not going to go through the projects— there are lots of projects underway, and there are actually even more.

The office is really affecting public health by helping coordinate this interagency agreement Dr. Beland mentioned a lot about, especially in toxicology risk assessment, providing some of the data and also the nanotechnology core.

DR. HINES: Paul, you mentioned Fred's group an awful lot but what about the other divisions? Are you reaching out and using the expertise in those other divisions as much or is it primarily the biochem tox group?

DR. HOWARD: Yes we are, but just think— most of the work we're doing in support of the agencies and with the National Toxicology Program rotates around the 2-year bioassay with rats and mice.

By default, it really is going to be supported in large part by, or it will be consistent with Fred Beland's division, being a more or less a cancer bioassay or a mechanism of cancer division.

But other divisions are involved. Martha Moore's group has been involved with quite a few projects—probably three or four projects where there are *in vitro* or *in vivo* mutagenesis fed into the data, and there are studies being conducted in Fred's division. Several of the studies have been conducted in the division of neurotoxicology.

It's going to change and get bigger because the NTP is changing. It's not just cancer bioassay, count the animals and count the tumors— it's really moving. For instance, yesterday Robert Sills, the Director of the Molecular Pathology and Pathology Group, wants to come here to have much more interaction and conversation with us regarding our imaging capability, which they see as a way to go into the future. It has been traditionally more cancer bioassay but it is changing and it will involve more of the divisions around here.

DR. FARRAR: It's my first time here so, excellent presentation. Thanks, that was very helpful. We have multiple centers in the foods program—CVM, CFSAN, ORA. Is there currently a mechanism for prioritizing the chemicals that come forward from multiple centers, even within a specific area like

acrylamide, for prioritizing the specific research needs within those?

DR. HOWARD: One thing I just couldn't do because I didn't have time was talk about this whole nomination process, like Dr. Hanig mentioned TEMPO. Actually, CDER came to me and said, we think we have a problem. They had already been working with Martha Moore and they said, we really think we have a problem.

What my office does, Robin Stingley's office, is we put together a literature review in a package for an FDA committee. We look at it and say whether or not it is worth addressing with the NTP. In this case it's going to be an obvious yes. Then that nomination goes to the NTP and I work with the NTP staff on the need, or if the work is already underway with the NTP and I just didn't know about it. We put together the package, and then it goes before their board of scientific counselors and I defend it all the way through. So there's a prioritization to some extent.

DR. FARRAR: But that's after it comes to you. I'm talking about on the front end as it's coming to you or before it comes to you. Are you aware of how that works?

DR. HOWARD: I'm going to be at CFSAN in two weeks giving what we call the dog and pony show about our interaction with the NTP and how it has benefited CFSAN. From that I know

people are going to come up to me and say, “I think we’ve got a problem with this or that.”

I don’t triage it at that point. We just start developing the nominations and let the process and take off from there. If CFSAN is just really gung ho about something like Dr. Beland’s furan studies, and they need this data for risk assessment then I hear their case and we push it so it gets a higher priority. I hope that answered your question.

DR. HANIG: Actually, I have two questions, one of them technical, the other sort of management. With respect to the nanomaterials, have we come to a conclusion as to whether or not the nanomaterials, on a dose-response basis, obey a molar concentration or are they different in comparison to the same materials that have an ordinary particle distribution?

DR. HOWARD: The conference I was at last week was on nanomedicine and AIDS therapy and AIDS treatment. I chaired the session and one of the people I recruited for that session was Gunter Oberdorster from the University of Rochester. He has data that addressed your question.

If you take, for instance, titanium dioxide and take 50 nanometer and 150 nanometer particles, and then instill it in the lungs you’ll get a dose-response of information. If you plot it based on their size, 50 nanometers versus 150, you get two totally different curves. If you base it on particle number, you

get two totally different dose-response lines. But when you correct the data based on surface area, all the data lines up along a straight line. There, the inflammatory response of the cells is a function of the surface area. You would predict that. You would not predict that *a priori*.

DR. HANIG: The nanomolar concentration.

DR. HOWARD: How do you express molarity of a particle? The thing that we're learning about nanomaterials within the agency and outside it with our collaborations with the OACD, is that you really need to understand every piece of information so you can plot the data based on mass, volume, surface area and particle number. Plot the data and then understand what kind of dose-response relationship you have. Right now, the question is out about how nanoparticles are interacting with tissues themselves.

DR. HANIG: The other question was that the Office of Scientific Coordination seems as if its focus is mostly on NTP-type projects, but I was kind of curious as to how the office relates to NCTR with respect to strategic planning and the relationship of the different divisions because there always is a tendency to form silos amongst divisions. I was wondering whether the office was involved in priorities, in general, and in strategic planning?

DR. HOWARD: Yes. I sit on Bill's coordinating council so I hear the higher level of what's happening with our resources and personnel, et cetera. Also, I interact with Dr. Beland and other division directors to let them know what else is coming.

About 6 months ago, I went to Fred and said TEMPO is coming. I gave him the preliminary literature analysis. So he knows it is coming and he can start thinking about who is the best in the division.

With others, there is an interaction with the division directors and when we think it's going to impact their division. I can think a year or two years down the road knowing the time it takes these things to percolate in and come into the center.

DR. HANIG: That's with a non-NTP hat.

DR. HOWARD: No, that's with my NTP hat, knowing what the centers are wanting, what NTP is going to consider for approval, and in what divisions.

DR. HANIG: What I'm really addressing is the non-NTP hat of the office.

DR. HOWARD: The non-NTP hat of the office is the nanotechnology core. That is really the non-NTP. Everything else is the NTP side. We just didn't know where to base nanotechnology so it's being developed as a core facility. Bill,

have we really had core facilities out here? I don't think we have.

DR. SLIKKER: We have, but they haven't really been called that.

DR. HOWARD: This will be a resource for all of the divisions. For that reason it's sort of sitting in the office right now.

PARTICIPANT: I just had one quick question that was directed to the glucosamine but probably has implications elsewhere as well. Given the difficulty in extrapolating animal data to human behavior and given the extensive use of glucosamine to date among humans, can't you rely substantially on epidemiological data as a means of assessing the issues as opposed to having to mount a large animal model system?

DR. HOWARD: The quick answer is no. The epidemiologic studies don't have the power to really address specific subset populations and their risk unless you really know there are subset populations at risk.

Glucosamine dosing is changing. For several years in Europe, they've been using a bolus high concentration dose of glucosamine. You take that in a liquid form and you get a much steeper Cmax on the AUC, whereas in the U.S. we've been taking these pills and we do not reach anywhere near the Cmax and

amount of AUC you get in the European. But that's changing in this country.

They're marketing it differently in this country. Work that Julian Leakey has done has shown, and this is the key, that serum levels in the animals are equal to the serum levels in humans. They are seeing the effects.

With all these studies, with Dr. Beland's studies, and others, you have to know the target tissue dose. Dumping in glucosamine, and dosing more and more just to get an effect—that's last year's studies.

Now, and this is a direction from Linda Birnbaum at NIHS to all the NTP, is understand target tissue dose and target cell dose symmetry so you can make that translatability into the human situation. But in this case we have a moving target.

I think hydrochloride and glucosamine sulfate concentrations are changing. So the epidemiology studies that are retrospective are not reflective of today's products.

Agenda Item: Division of Veterinary Services

DR. CARRAWAY: I'm Jeff Carraway, the Director of Veterinary Services. Not a lot has changed since I talked to you last year but I have a couple of ideas to tell you about.

My group manages all the animal facilities, all six of the animal facilities here at NCTR, and a pretty complex animal care and use program. We provide animal care, veterinary care

for nonhuman primates, and dye preparation for services, primarily through a contract with a Bionetics Corporation.

A lot of our time is spent in IAC activities, institutional animal care and use committees, review protocols, reviewing of the facilities and programs, tracking the animals, ordering the animals, and that type of thing.

As time allows and opportunity arises, we enjoy participating in research activities as either investigators or co-investigators. We are liaisons to the regulatory agencies, ORA, USDA, and also to American Association for Laboratory Accreditation Committee (AALAC) .We're excited about a new laboratory animal medicine internship program we're participating in with UAMS. I'll get to that in a minute.

Our group consists of just 3 government employees but 66 contract employees. I'm the vice chair of the NCTR Institutional Animal Care and Use Committee (IACUC) and the attending veterinarian for the facility, and also the contracting officer's technical representative for the contract. You see all the services offered by the contract.

Dr. Gopee is a clinical veterinarian responsible for the veterinary care of rodents, our swine, and our zebrafish. All animal orders have to go through Kathy Miller, and she also tracks all of the animal use that are involved in the approved protocols.

NCTR has been AALAC accredited since 1977 and that demonstrates that the research programs not only meet the minimum standards required by law, but are also going an extra step to achieve excellence in animal care and use. Accreditation has to be reviewed or renewed every three years. We just had our triennial review this past summer and I'll tell you about that in a few minutes as well.

We're also proud to be institutional members of the American Association for Lab Animal Science. It is the premier forum for exchange of information and expertise in the care and use of laboratory animals, and ALAS does certify technicians, managers, and supervisors.

We place a strong emphasis on our technicians in becoming ALAS certified. They have a financial incentive to do that on a contract. In other words, certified technicians make more money than non-certified technicians.

In the left hand column there, ALAT stands for Assistant Lab Animal Technician, then Lab Animal Technician, Lab Animal Technologist, Certified Manager of Animal Resources, and we're especially proud of our CMARs because getting that particular certification is especially grueling. We like to have around 90 percent of our technicians certified, and we always get a lot of kudos from ALAT because of that.

Just a simple depiction of how the contract positions are organized—every animal facility is run by a supervisor and every facility also has one or more technical specialists that really are the logistics coordinators for all the states. They're overseeing the down in the trenches work that the technicians are performing.

Our technicians, assistant technicians, and production aides are all part of a bargaining unit, so it's a unionized workforce. Product aides or entry level positions that drive forklifts and work in the processing area are kind of in training to become technicians.

We have about 112,000 square feet of animal space in about 6 facilities. We have a nice rodent production facility where we have a specific pre-colony path we've had here for 38 years. So the strains produced in that colony truly are NCTR sub-strains.

We have three conventional rodent facilities, two large and one small. One room in the Building 53 facility houses our new zebrafish. We also have a phototoxicology center, which hasn't been active lately and Dr. Howard didn't mention anything about it, but he's been the lead scientist in that center.

We have a very active nonhuman primate research center, which I think Dr. Paule will probably tell you a little bit more about tomorrow. We're excited about that facility

undergoing renovation and expansion. We're expanding it from four rooms to seven rooms. It's also adjacent to the imaging facility, which I think Dr. Paule, and probably Dr. Slikker, will tell you more about, but I don't know if he has said anything about that. You'll hear more about that later. There's a lot of nonhuman primates that are going to be involved in our studies.

We don't have the use of BSL-3 facility for animal studies yet. We do have an avian influenza study, though, that's coming on board next year and we're going to house animals in ventilated cagings to do that experiment there.

Our animal care program is primarily concerned with taking care of animals everyday, sanitizing the facilities but, of late, the contractor has been asked to perform technical procedures more and more. I think this morning, the DEEHP study was mentioned in which we had to do IV injections in four day-old rat pups. Everyday, we had to inject the rat pups, and that's pretty tough, but we did it and it was successful.

I know you can't see this very well, but I just want to give you an idea of the variety and the number of technical procedures we perform. This is a report from a couple months ago. What jumped out at me was the 19,722 gavages we did that month in rats on the furan study.

Like I said, we have a rodent production colony that's unique; it's been here for 38 years. They are unique sub-strains. We're very careful about keeping pathogens out of that colony, of course, because most of our studies apply from this operation.

We have an intensive health monitoring program—much more intensive than animals in the conventional housing areas. To protect those animals to pathogens, we're housing them in individually ventilated caging systems.

As I mentioned, our nonhuman primate research center is quite active. A lot of behavior testing goes on in there. We have a timed breeding program that supplies pregnant animals and infants to several of our studies. Again, Dr. Paule will probably say more about this center tomorrow.

The new thing on the block for us is the NCTR zebrafish facility. It is actually one room, and when this thing was set up, it was quite a challenge for us because we didn't know a thing about zebrafish. Most of us still don't, including me, but with Dr. Kanungo's help we got it going and flowing. This lady on the far left here, Melanie Newness has become our chief technical specialist. She's become our zebrafish expert.

We have the capacity to hold about 5,000 of those zebrafish but I think we're going to keep it down to about 2,000. I think there are about 500 in there now. As you can see

from those pictures, it is a fine-tuned, complex system. When I go in there I don’t touch anything. Even feeding these critters is complicated and, of course, the study unit, the experimental unit, for zebrafish, is the embryo. So it’s our job to maintain healthy animals, breed them, and produce eggs for the research.

My understanding is you take two males and two females when it’s time to breed them, transfer them into a breeding tank and leave them overnight. Now 30 minutes before daylight, the eggs will be produced. We come in, we collect those eggs, put the males and females back in their regular cages, and ship those eggs upstairs to Dr. Kunungo’s lab.

Of course the provision of first rate veterinary care is a high priority for us. We have 3 board certified veterinarians, two of us in laboratory animal medicine, which is a specialty in veterinary medicine, and Dr. Gopee is board certified in toxicology.

We are proud to be research team members. All of us have research degrees and we, like I said before, encourage and look forward to participating in research projects.

We’re fortunate to have a really well trained technical staff that looks at animals every morning and gives us a call right away. We can go over and see those animals immediately.

As Dr. Cerniglia had mentioned this morning, we are also fortunate to have an on-site, in-house microdiagnostic lab. We rarely have to send anything out. We can immediately send samples over to micro and get them analyzed—also true for pathology.

Pathology used to be under my division, and I used to say something about it but I left it out this time thinking Paul would say something. Though he didn't, we do have a great on-site pathology lab.

Providing healthy animals and keeping them that way is the heartbeat of our mission and we do a lot of health monitoring, a lot of environmental monitoring, a lot of sampling and testing to make sure those animals stay healthy, and a lot disinfection of facilities and the surfaces. We quarantine every animal, regardless of where they come from, even from commercial venues. A lot of places don't do that. We even vaccinate our rhesus monkeys for measles and we feed our rodents irradiated diet, so we go to great links to make sure that our animals are not exposed to pathogens.

We, not only, want to keep our animals healthy but we want to keep them happy. Environmental enrichment is a real hot button issue these days in laboratory animal science. The primary aim is to enhance well-being through stimuli,

structures, and resources that facilitate the expression of species' typical behaviors.

We put perches in cages for primates, shelves in cages for cats, nesting materials for mice, mice like to mate in this, and rats like to chew on things so we give them some nylabones and things like that, as well as toys for monkeys.

We also like to provide some sensory and motor stimulation, and we have a very extensive behavioral testing program in the primate colony, which we consider as environmental enrichment. We haven't tried music or television yet.

Also, we provide shelters for animals in case animals are fighting and they want to escape into a shelter. The mice also like these little igloos where they can take their nests in there, build them, and have their babies in that protected shelter.

Another unique thing about NCTR is we have a really nice, big diet preparation facility. As you can see from that list of equipment, we can produce just about any large-scale production of dose water, dose diet, dose creams, whatever you want to. So not only do we receive and distribute and process regular animal feed, but we can also mix test articles in diet, in water, and wash solutions and dose creams. And, we can make those in very large quantities and to exacting standards. It

seems to go in cycles. Right now we seem to be producing a lot of gavage solutions, and that's primarily for the BPA and the furan studies.

As I mentioned before we're really excited about participating in our laboratory animal medicine internship program. I got a call the first of the year from Doctor Randolph at UAMS. She heads up the lab animal resources operation there, and wanted to know if we wanted to participate in an internship program with UAMS, the VA Hospital, and the Arkansas Children's Hospital. Of course we did, and that began in July.

In fact, Veronica Yary, the first student, is here this month. She's sitting right back there I think. She'll go through a three month rotation at each institution. So we're excited about having her. She gets exposed to primates and zebrafish here, which she wouldn't get exposed to at any of these other institutions. She also has rotations through our pathology and our microbiology divisions.

IACUC activities take up a lot of our time. We're the point of contact for USDA and ORA. We prepare the reports for them and any other correspondence. We're also a point of contact for AAALAC. We host the site visits for them every two or three years.

That leads me right into our site visit, which we had this past July. We were fortunate to have an AAALAC council

member emeritus as the lead site visitor. We're told that site visits led by these council members emeriti are limited to those institutions that have demonstrated a long term commitment of achieving and maintaining high standards of laboratory animal care and use, so we were really happy about that.

This guy was really interesting. He doesn't own a cell phone and he's the senior champion race walker for South Dakota. We had a typical agenda. They were here for two and a half days. The first morning they did the program description review, then we inspected the facilities for a day, had lunch with the ICAC and that kind of thing. The last morning was document review, and then we went to the exit briefing where they're supposed to tell us the good, the bad, and the ugly.

The first thing out of his mouth was that we had no mandatory items. This was great news. He told me later, he said, "you know when I usually tell a group of people that there are no mandatory items there's a lot of clapping and hooting and hollering going on." We just sat there in stunned silence. I told him later that was just our strange way. We were happy.

They did note some outstanding program components as you see there. Our documentation was excellent, good research and support staff training, great occupational safety and health program—we always get commended for that, and they really liked our zebrafish facility. We're going to have to keep it nice and

clean for next time. They saw no sick or injured animals, which reflected an excellent animal husbandry and veterinary care program and, of course, we got kudos for our facility sanitation and management.

Now, he pretty much told us, which is unusual, we were going to get full accreditation. What happens is the AAALAC council meets three times a year, and they just met in September. Until we hear from them we don't know for sure officially that we have full accreditation but we do expect it and, actually, I expect to hear from them any day now because I know they met in September. We're really happy about that. We're going to get another three years of accreditation. That's all I have for you. Any questions?

DR. DOW-EDWARDS: A very nice presentation and congratulations on a wonderful facility here. It's great. My question relates to the environmental enrichment. You mandated additional environmental enrichment and I'm concerned if you and the various PIs have considered the effects of this enrichment on the behavior of the animals and how this relates to previously collected data.

DR. CARRAWAY: That is a concern. In fact, I didn't mention it. Since you brought it up I will now. The NTP program will not allow any environmental enrichment, so the great bulk of our work here is NTP so none of that's happening.

On the animal care and use forum that all the PIs fill out, they have the option to check "I'll take environmental enrichment or I won't." But you have to scientifically justify why you won't and, of course, the scientific justification is, "hey, I've done all these studies before I was using this stuff so I shouldn't have to use it now. How it's going to affect my data?"

DR. HINES: There is a lot of effort to do cross-breeding with the various different strains of mice to recapitulate genetic diversity within the human population. Is there any effort at all going on at NCTR to develop that kind of resource there?

DR. CARRAWAY: Not to my knowledge. I haven't heard anything—if Paul wants to comment on that.

Dr. HOWARD: Since we're involved in the National Toxicology Program there's a really large effort there to understand mouse strain, specifically issues in toxicology. We're involved in that program as well.

PARTICIPANT: That's what one of our groups of the NTP is looking into. That's one of the important things we're looking at.

DR. WATKINS: Can you give me an idea of how saturated your services are, so if I wanted to do a rat or zebrafish study

would I have to wait months? To what extent are these services rate-limiting?

DR. CARRAWAY: That's really a timely question because in the past at NCTR, we have a contract staff that has usually had plenty of people and plenty of resources to perform all the services, even as they come along. So, there was very little planning that was really necessary. But lately, in the last two years, we have been packed. Our animal facilities are full. In fact right now, yesterday I think, we just filled up our last animal room we had in building 53. So, yes, as these studies come along and researchers want to start adding on to that, at this point we're going to have to say, look we can't start your study right now, we just don't have the room. We never have done that, but that time is coming here.

PARTICIPANT: Another issue that we always have to address here is pathology. We really haven't talked about pathology today but we love these studies and we always have to take animal care into consideration, but another limiting factor is how many animals we can put into pathology and how many they can handle at one time. So that's all coordinated right at the beginning before we can even consider looking at studies.

DR. CARRAWAY: Of course, that has to be coordinated with animal care as well.

DR. ASHLEY: Does your staff do the actual exposures? Does that fall within your facility there or is that within the different divisions?

DR. CARRAWAY: When you say exposure—administering the test articles, that kind of thing?

DR. ASHLEY: Yes.

DR. CARRAWAY: Yes. The technical group, save these gavage studies on BPA and furan, does actually do the gavaging of the product.

DR. ASHLEY: Is it just gavaging? Do you do skin painting? Do you do inhalation exposure? What are the options?

DR. CARRAWAY: We haven't done any inhalation exposure that I'm aware of in years, but any technical work that is a requirement of the study, the contract people usually do unless the research group has the option of doing it and they want to. But it's become pretty much routine for the technical group to get up to speed if something is new or, of course, perform routine things like gavage, injections, and things like that.

DR. HANIG: I just had a couple questions about the animal models. Have you ever considered using micro-pigs because of the size issue of many pigs not really being mini and getting very big?

DR. CARRAWAY: We don't use micro-pigs because those mini pigs get over 100 pounds.

DR. HANIG: I’ve heard that they get bigger than that. The other question is have you ever used, considered using, or even have the space to have dogs? They’re very good for pk and cardiovascular and, in certain instances, cats are terrific for neurological studies.

DR. CARRAWAY: When I came here 20 years ago there were 5 or 6 dogs here, and they were here for about a month and they were gone. We’ve never had any since. Of course, it’s just whatever the research staff needs and what models they need. It hasn’t come up—dogs or cats—but for pigs, we have a very small capacity right now. We only have 12 cages, so we’ve had 2 or 3 pig studies. I think another one is coming up this year. You’re right. I would love to use micro-pigs.

DR. AFSHARI: Thank you very much. I would like to introduce Dr. Beverly Lee Cook, who is going to give us an update on the Women’s Health Program.

Agenda Item: Women’s Health Program

DR. COOK: Good morning or good afternoon. I am going to be very brief, because I know I am standing between you and lunch. What I am going to do today is just give you a brief overview of the Women's Health research activities here in NCTR.

In November of 2008, I was asked by Dr. Slikker to act as a coordinator for these activities. I also serve as the NCTR-

FDA-Office of Women's Health liaison, along with Becky Simmons in the Office of Planning and Resource Management.

Why is there such an increase in women's health and why is it important for FDA? Women are disproportionately affected by several conditions and diseases, in terms of incidence, diagnosis and response to diseases. Traditionally women's health research was thought, pre-1990, as diseases and conditions specific to women such as contraceptives, pregnancy, female reproductive system, and breast cancer and ovarian cancer.

Now, because of the lack of women in clinical trials, a number of women’s health research advocates got together and a number of task forces began as early as 1986. An NIH guideline was prepared to include more women in clinical trials. However, in 1990 a GAO report realized that NIH guidelines were not being followed for some of the large clinical trials, particularly for heart disease, aging and HIV/AIDS. In 1992, the GAO report also showed that women were still under-represented in studies for some drug classes, such as cardiovascular drugs, and there was no analysis for sex and gender differences in these studies either.

In 1994, the FDA, by Congressional mandate, formed the Office of Women's Health. At that time, NIH also had the Office of Women's Health, and FDA formed theirs in 1994.

Their mission at that time was, through policy, science and outreach, to protect and advance women's health research, to

advocate for an inclusion of women in clinical trials, and to analyze the effects of sex and gender. Later, the FDA Office of Women's Health supported FDA scientists on projects aimed at protecting and improving women's health.

In 2003, the Institute of Medicine report entitled *Exploring the Biological Contribution to Human Health: Does Sex Matter?* was published. In this report, it was found that there were male and female differences and descriptive types of studies in disease, and in response to various pharmaceuticals. Also in this report, it was suggested that more mechanistic types of studies were needed to further address these issues.

In that report, there was clear terminology to distinguish between gender effect and sex effect. Sex was defined, in this report, as a classification of living things generally as male or female according to their reproductive organs, and functions assigned by their chromosome complement. Gender was a person's self-representation as male or female, or how that person is responded to based upon their gender presentation.

As recently as September of this year, the 2010 Institute of Medicine still finds that there is a lack of women's health research as it relates to various other diseases. In this report, entitled *Progress, Pitfalls and Promise*, it finds that women's health research, although there has been a tremendous

increase and progress in this area, still lacks a lot of conditions that have seen only moderate change, or in some cases, little or no change in these effects.

One of the major IOM recommendations is that all research should be designed and conducted in a way that allows for the analysis of differences between men and women, and further that incorporation of sex and gender differences into the design and applications of new technology, medical devices and therapeutic drugs, and actualized, personalized prevention, diagnosis and therapeutics for women. In other words, continue to move away from one size fits all models.

What is women's health today? Women's health today has an expanded view. It is any factor affecting morbidity and mortality in women across the life span. I would like to repeat that again, because I kept hearing that we have to consider, when we look at these studies, the life span. This can be in cardiovascular diseases, epidemiological diseases, AIDS, diabetes and of course all cancers except those related to males. So, we are moving from a more descriptive type of research as was stated pre 1990 into a more mechanistic understanding, using some of the technology that is available today.

At NCTR, when I was asked to coordinate this activity, we are researching as if we are scientists within all of the divisions, or collecting or conducting research in women's health.

In addition to conducting research, they are collaborating with the centers such as CFSAN, CDER, and CBER, and also we have studies proposed with CPTA, the Tobacco Products Center, CDER and also ORA.

The reason to form this working group at NCTR is to be under the Office of the Associate Director of Regulatory Activities, because that is a liaison to serve the centers in Washington, along with the scientists at NCTR. The mission of the working group is to increase emphasis on mechanistic women's health research, foster collaboration among NCTR investigators, develop cross-center and cross-agency research projects to address women's health needs, to provide opportunities to mentor young investigators in this area of research, and to share this information with the FDA Office of Women's Health.

That occurs through a series of intramural seminars with the scientists here at NCTR conducting research in these areas. This gives you some of the areas we have had in the past. We also conduct an extramural seminar series, in which we brought scientists from the FDA to NCTR. Last year we had our NCTR women's health and safety day. We had a female speaker from the Center for Drugs, and we also had CFSAN. We focused on those centers at that particular time.

Through this coordination, we would like to build upon the existing infrastructure within FDA with the centers in

Washington, utilizing all of the omics technology you heard about today within a different division, the translational biomarkers, drug efficacy and safety, bioimaging, nanotechnology, microbiology and personalized medicine, in order to increase our women's health research focus.

These are some of the focus areas in which we have funding from the Office of Women's Health from 2009 to current. As you can see, we are very diverse within the division. We have hepatotoxicity, bioinformatics, epigenetic, carcinogenicity, microbiology, personalized medicine and nutrition, pharmacogenomics, and in the spring of this year, we had two more projects added, systems biology and microbiology for the environment.

As a result of this coordination starting in 2008, it has increased submissions and increased the interest of scientists at the centers in women's health research. In FY11 we had a very high number of concept papers. We had a total of 14 that were conducted by the scientists at NCTR and submitted to the FDA. Out of the 14, seven of those concept papers were selected and are now being developed into four proposals. Once the concept papers are submitted, we have an ad hoc committee here at NCTR who will write those concept papers, and along with the ranking at NCTR and the ranking at the FDA Office of Women's Health, they will select

those concept papers based on the FDA's need of which will be developed into protocols.

As you can see for FY11, a number of these concept papers come from all of the divisions. This year, we have two from neurotoxicology, one from personalized medicine and nutrition, one from our group, one from biomedical toxicology, one from genetic and molecular toxicology, and one from systems biology. So the effort that started in 2008 is increasing the visibility in this area of research at NCTR.

From 1994, all the research has been conducted in women's health research here. We have had a total of 34 grants funded totally, totaling approximately a million dollars in this area.

Last year, I had a grant from the Office of Women's Health to fund a workshop. This was to bring visibility to the women’s research conducted here to increase other areas of women's health, in addition to cancer and toxicology. That was the main focus for NCTR.

So this workshop objective was to first identify critical gaps in FDA regulatory research agendas, addressing disparities in women's health research as it relates to incidence and response to medical products, to foster interaction between the scientists from regulatory centers, universities and NCTR scientists, and facilitate the development of collaborative

projects. We reported the findings from the workshop to the FDA Office of Women's Health to further assist in defining the potential research needs and establish a future health research agenda.

The title of that workshop was "Sex Differences in FDA Regulated Products." It was held September 2 of this year in Little Rock, research for the future. The focus area was autoimmune diseases, cardiovascular diseases, mental health and drug-drug interactions. We were right on target with that workshop.

I attended the FDA workshop on September 14. I also attended the NIH 20-year celebration. These are still the focal areas in which we really need research to further address sex differences.

The workshop outcome: We are developing a white paper with the FDA Office of Women's Health to further discuss proprietary areas of research. We will use, in addition to the outcome of that research, the 2010 IOM report to discuss strategies for addressing critical gaps in sex differences in current FDA-regulated products. Also important, are future anticipated gaps to improve women's health that will ultimately benefit the whole public.

Sex differences throughout the life spans are prevalent and may impact the risk-benefit analysis for products regulated by

the FDA. Therefore, FDA research is necessary to support decisions in public health. FDA reviewers and research scientists continually look to ensure that both women and men are protected from adverse reactions to drugs or devices, and that the food is safe.

Attending that FDA 20-year celebration, made us also want to look forward at the next 20 years. These are some of the research visions for the 2020 women's health research, looking at the FDA workshop along with our workshop. We want to increase sex difference research across the entire research spectrum as it relates to FDA-regulated products; incorporate findings of sex-gender differences and the design and application of new technologies, medical devices and therapeutic drugs; develop comprehensive approaches to personalized medicine that take biological sex, age, and factors such as social and cultural influence into account. I think Dr. Kaput talked about that this morning in his presentation. Create strategy alliances and partnerships to maximize both the domestic and global impact of women's health research as it relates to clinical trial inclusion and safe drugs to protect the public.

But in order to carry out these goals and to continue to increase the visibility in the research area for women's health, scientific collaboration between government agencies such as NIH,

FDA and CDC, along with academia and industry, is greatly encouraged.

At our workshop, I failed to mention that we brought together MDs and basic scientists as well as representatives from the pharmaceutical industry. So this is the three-pronged way for the future to promote this area of research, but also focus in, as Dr. Kaput also stated, on both extrinsic and intrinsic factors, in addition across the whole life span.

I think I got through, sorry for this fast coverage, but I am available to answer any questions.

PARTICIPANT: I will open it up to questions. Scott?

DR. BURCHELL: I was very pleased to see that you had autoimmune diseases on the top as a focus area, because this is something that is very difficult to address, but is important. I think the Center could make an impact on that with some of the exposures because you have to develop models to address some of those issues. So I was pleased to see that.

PARTICIPANT: That is one of the areas we find a lot of women affected by a number of those diseases, such as MS and lupus, to try to entice the scientists. We had an increase in concept papers, so we are beginning to look at these different areas.

DR. DOW-EDWARDS: I commend you for your efforts. I do sex difference research and I have been doing it for many, many years. It is a vast sea out there.

My question is basically, if you have investigators that are not cooperative in looking at sex differences or gender differences, how do you realign their motivation?

PARTICIPANT: Dr. Slikker?

DR. SLIKKER: Beverly and the group has done a wonderful job in doing this, because they have found a way, by working with the FDA's Office of Women's Health, to provide an enticement in terms of real money to do some of these studies.

And of course other ways are involved as well. As you know, most of the National Toxicology Program studies and others are going to rely on at least two sexes, oftentimes, to be able to do these kinds of studies. So males and females are used for those studies to be complete. But Beverly, you probably have other ideas to add to that.

PARTICIPANT: Also, at the 20-year celebration when I was there at NIH, it was also encouraged to form a partnership between NIH and FDA. Talking to a lot of the universities, I think we can increase the funding for the science. I have already talked to some of those scientists. The 14 concept papers, I thought, was great, and they only selected seven because of the limitation of funds at the NIH level. But I have talked with some

of those scientists; perhaps we can get that funding through other mechanisms.

PARTICIPANT: Any questions from the FDA Center reps? I think we will adjourn for lunch.

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

Agenda Item: Presentation on the Center for Tobacco Products

DR. ASHLEY: Thanks for the opportunity. Just to give you a tiny bit of history on me; my name is David Ashley. I spent 27 years at the Centers for Disease Control and Prevention. The last 15 of those years were spent doing tobacco research. I am a lab guy. I am an analytical chemist. We spent 15 years taking cigarettes apart, testing them, smoking them, measuring biomarkers, and doing everything we could think of with cigarettes.

Four months ago I moved to the Center for Tobacco Products and became the Director of the Office of Science. It is a different world at the FDA than it was at CDC, but it is an exciting world. I wanted something different, and that is what I got.

The presentation basically is going to be four parts. First, I will give you a little background on tobacco and tobacco products, and why are we doing the regulation in the first place.

Some of it may be obvious. I assume some of it is not going to be so obvious, at least I am hoping some of it won't be. I will talk about the purpose and give you an overview of the legislation so you know what is really in there. I am going to talk about what our accomplishments have been to date, and then capture the role of science a little bit, and show how science plays a part in all of this.

Our public health goals in the Center for Tobacco Products are, number one, to prevent youth tobacco use. If we can stop kids from starting to use tobacco, the epidemic will run away, it will end, it will stop. So that is the number one priority.

The second is to help adults who are using tobacco to quit. That is a bigger challenge. Third is trying to promote public understanding of the contents and consequences of the use of tobacco. We really want to try to educate people so they understand more. We hope that if you educate people and they understand more, they will do the right thing. Maybe that is a wild hope, but we hope that will happen. Fourth, we want to develop the science base to understand the real science we need to make meaningful regulatory decisions.

A little background: Tobacco use is the leading preventable cause of death in the United States. About 440,000 people every year die from smoking. About 50,000 deaths occur

yearly in non-smokers due to exposure to secondhand smoke. There are 8.6 million smokers who have at least one serious illness due to smoking. This is a lot of people, this is a huge population. Smokers who die lose about 14 years of productive life. That is a major loss. For every death, there are another 20 Americans who suffer from a tobacco related disease or disability, and there are about $193 billion lost every year due to medical costs and production losses.

After decades of progress, for many years since the 1960s when the first Surgeon General's report came out, the prevalence of tobacco use in the United States has been dropping. It has been dropping steadily, until about 2004. Starting in 2004, things began to stall out. We have another data point on here that has come out recently. Still, we are stalling out at about 20 percent. Things are not going down anymore. Something we are doing is not giving us the impact we need to have. The Healthy People 2010 goal was to drop this down to 12 percent, and we are nowhere close to that. Because it has leveled off, we are not making the necessary progress.

I predicted an idea of what is going to happen in the future; cigarette smoking amongst ninth through 12th graders will still show the same thing. It is not changing, either. Kids are continuing to smoke. We have it down again to about 20 percent, but it is not getting down to the 12 percent we were trying to

achieve. So we have to do something different. We have to have an impact to drop that down. Otherwise we are going to stay right where we are.

Twenty to 25 percent of high school students report current use. Four thousand kids start smoking and a thousand kids become regular smokers everyday. So we are losing 4,000 kids everyday. Ninety percent of adult smokers start smoking as teenagers. Adults generally, though there are a few exceptions, don't start at the age of 30 and say, that is an awful habit, I think I will take that up, I know it will kill me. They just don't do that. Most adults have reasons not to do that. So 90 percent start as teenagers. There are a few adults who start later, but 90 percent start as teenagers.

Mainly, kids become addicted before they are old enough to know better. That is one of the principles we go by in the United States. Promoting tobacco really does lead to youth smoking, so that is a huge deal.

On the other side, not the use side but the tobacco side, tobacco products are a moving target. They change constantly. They are all over the board. Around 1955, the introduction of filers and porous paper, reconstituted tobacco came into play. In 1970, they introduced tip ventilation into the product. I would love to sit and give you an hour long lecture on tobacco products, but I'm not going to be able to. You can ask me

about these later if you want. Around 1975, they introduced expanded tobacco. So these things are changing constantly.

Cigarettes are not just cigarettes. They are a very complex, highly engineered device. People don't know what they are getting themselves into. The tobacco companies clearly do.

These are ventilation holes. You can see them right there. Virtually every product, every cigarette, has a number of holes in them. They have different numbers of holes. Those holes are all that stands between a full flavor cigarette and an ultralight cigarette. That is the difference right there, holes. We put holes in so the holes stay outside the machine when we test, and that is all. They put holes in there to beat the test. So when we develop testing, we have to come up with ways to beat the product so we can determine what the product is really like.

Cigarette filler contains a mix of components. In the United States we have what is called the American blend. The American blend includes bright tobacco, burly tobacco, stems and ribs, Oriental tobacco and reconstituted tobacco. Reconstituted tobacco is a very interesting thing. That is what results at the end of the day when they scoop up all the dust, the insect parts and all the junk. I am learning a word at the FDA called filth. It is a very interesting word. They scoop up all the filth, and they put it together. They make the tobacco sheet, they cut the

tobacco sheet up and they introduce it back into the product. That is what is called recon. Recon has a history all on its own.

In addition, some studies have come out recently saying that nicotine levels have been changing. The tobacco industry has been altering the nicotine levels over time. This is work by a group at Harvard who looked at nicotine levels in the products between 1997 and 2006. There is an upward trend in nicotine levels.

Another big difference: It is not just the nicotine. It is not just the addictive properties, but the toxic properties of the compounds of the cigarettes have also changed dramatically. These are data from my laboratory in CDC before I came here; it looks at carcinogenic nitrosamines and the variation between cigarettes bought all around the world. We measured carcinogenic nitrosamines in those cigarettes. The red bars are Marlboroughs and the green are the local brand.

For carcinogenic tobacco-specific nitrosamines, levels in Marlborough are much higher than levels in local brands. It has to do with the blending and curing of the tobacco. I can't go into all that detail, but cigarettes are not just cigarettes. Cigarettes vary tremendously.

What does the Public Health and Tobacco Control Act do for us? The passage of the act is a significantly new component. There is a lot of tobacco control going on, and tobacco control

needs to continue. The act does not replace any of that, but it gives us new tools of what we can do to make an impact on the morbidity and mortality from tobacco use. It gives us new opportunities.

It established a new standard for FDA. The standard we meet in the Center for Tobacco Products is to regulate tobacco products based on a public health and population health standard. That is the standard we are working on. A lot of people ask, what in the world does that mean. It is a very good question.

The population health standard is that public health is influenced by effects on both the users of tobacco products and the non-users of tobacco products. It is not just the people using the products. It is also the people who are not using the products. So we have to deal with initiation; does the product itself increase initiation? Does the product stop people from quitting or cessation? Does the product make it easier for people to relapse or get back into it after they have stopped?

Secondhand smoke exposure is also important. Poly tobacco use is a huge issue that is coming. Poly tobacco use means, I smoke cigarettes, use snuff and other forms, and I use dissolvables all at the same time. I want to quit my cigarette, but instead of quitting my cigarette I am going to start using smokeless tobacco, and then I will use my cigarette when I want to. So we have to deal with a complex system.

The population health standard is reducing morbidity and mortality overall in users and non-users. If you have a tobacco product that is less harmful, that has reduced risk for the individual users, but ten times the number of people start using it, which is no good; that is not helpful. So we have to calculate both of those. That is what the population health standard is. We are not dealing with safety and efficacy. That is not what we are talking about. It is a population health standard.

The authority under the act: The act gives FDA the authority to regulate tobacco products which, by definition, are products made or derived from tobacco intended for human consumption. It does not include drugs, it does not include devices. One of the things that the FDA has not done yet is figure out what a tobacco product is and what a drug is; we have to make that decision. So FDA is trying to determine that to find that line.

FDA is the primary federal regulatory authority with respect to the manufacture, marketing and distribution of tobacco products. It is not just about what is in the product, it also has to do with marketing and how the product is sold to the public, because that impacts the population health standard. So it is not just the product, it is how we advertise the product,

how they market the product, and everything else involved with the product.

The act is modeled on device law. Much of the language was taken directly from device law. So we deal with premarket applications for new and modified risk products. We have postmarket surveillance, which is very, very critical in making all of this work. We have performance standards on the product we can apply, testing and reporting of ingredients, adverse event reporting, new warning labels, advertising and promotion restrictions, and user fees. Everything in the Center for Tobacco Products is paid for by user fees. FDA can't do anything related to the act that is not paid for by user fees, which is a very interesting thing when you are trying to work with people. Again, I am not going to go into that, but it does create major challenges in what we can and cannot do.

Section 904 talks about the submission of health information. Each tobacco product manufacturer shall submit a listing of the tobacco product ingredients that have already been done, and documents that have developed on health, toxicological, behavioral or physiologic effects of tobacco products.

We are constantly asking and getting reams and reams of health documents. A problem now is going through these documents and making heads or tails out of them, because there are millions of documents. From our last request, we got well over two million

pages of documents, and we have a very, very small staff trying to go through that. So that is a major challenge for us.

I don't think the companies are producing as many documents as they used to produce. Now that we have access to them, it seems the document production is dropping dramatically.

In addition, the Secretary shall establish a list of harmful and potentially harmful constituents. That is something we are in the middle of right now. Science has a major impact on that. The TSAC, scientific advisory committee, has identified the criteria for establishing our initial list. According to that list, there will be about 100 or so constituents on it.

There are 8,000 constituents in tobacco and tobacco smoke, so clearly we are not covering all of them. A lot of them are probably toxic and a lot of them are probably carcinogenic, so we have a long way to go, but this is just the beginning. It is a first step in identifying which constituents they need to report to FDA. We need someone who can do toxicology to help us with the other 8,000. So if you know anybody that does toxicology…

Section 905 requires all tobacco manufacturers to register. The first stage was telling us who they were; the definition of a tobacco manufacturer is interesting. It is not just Philip Morris who makes cigarettes; it is everyone else who makes the products that go into the things that make cigarettes. So it is the people who make the filters, the papers and

everything else that go into cigarettes. They are all product manufacturers.

They are subject to bi-annual inspections. We are a long way from doing that yet, but eventually we will be doing manufacturing facility inspections.

Section 907 talks about tobacco product standards. Tobacco product standards give us tremendous authority to create changes, but we have to have the science beforehand. Everyone in the tobacco control community assumes that you can just go out there and say you have to do this and you have to do that. FDA can't exactly do that. We have to have the science to support what we are doing. So that is one of the things we are trying to do right now, is develop the science that will tell us what standards to set. This is a big challenge but it has to be done, and this could have a huge impact.

We could force them to reduce nicotine. We could force them to reduce certain toxic components. There are a lot of things we can do, but we have to have the science to know what to do before we do it.

A couple of things we can't do: One, we can't ban a class of tobacco products. You can't say “smokeless has to be removed.” You just can't ban a complete class. You also can't reduce nicotine yields to zero, but you can come really close.

Section 910 talks about premarket review. This is built very much on device law. It is very much the same thing. We have a part that talks about products which are substantially equivalent, and we have been working on guidance related to substantial equivalence and applications for premarket review. They have to tell us about the health risks of the product. They have to list the ingredients. It talks about compliance with certain standards. And they have to give us the labeling. We have to look at the labeling to see if that labeling will actually encourage people to start using the product. So there is a lot of information we will address through premarket review, and they cannot market that product until we give them a marketing order.

Modified risk tobacco products: This is the section of the law that provides the biggest threat of doing harm. We hope it can be something that can be used for good, but it is something that can easily be used for harm. Modified risk is primarily about the claims. It is less about whether the product is safe, and more about the claims made about the product. If they can make claims that these products are safer, the question is, what impact will that have on people who have stopped using or on those people who wouldn't use normally. This is where the population health standard comes into play, around modified risk.

User fees: I am not going to talk about this a lot, except that we are paid for by user fees. We can't take money

from any other part of FDA, because when Congress put this together, they didn't want the Tobacco Products Center to be sucking other money out of the vital programs in FDA.

I'm not a threat to you guys, which is really good. Everybody is very friendly, because they realize I'm not taking any of their money away, which is very pleasant.

Cigarette labels and advertising: One of the first things you are going to see, one of the most visible things about the Tobacco Control Act that is going to come out soon, are the pictorial warnings on all cigarette products. This will be something visible. The public will see it, and the public will know that they are in a different world. No longer will you have that little tiny Surgeon General's warning on the side of the pack. You will have very clear, graphic, pictorial warnings. So this will be a lot of fun when it comes out.

We have new warnings on smokeless tobacco, right along with cigarettes, in advertising.

Time line: President Obama signed the act June 22 of last year. September 22, cigarettes with characterizing flavors other than tobacco and menthol were banned. November of last year, a final guidance was issued listing the ingredients of tobacco products. That came out December of last year. We had a draft guidance on health document submission, and that allowed us

to begin asking them to give us the documents they have, which they have dumped on us.

March of this year, broad, new regulations will decrease youth access. We have across-the-board laws nationwide, trying to stop kids from being able to buy cigarettes. We have done a lot of compliance work in that area, and that is, I think going, to have a major impact.

June of this year, smokeless tobacco health warning rotation was implemented, and in July we banned the use of light, low, mild or similar descriptors on cigarettes. I don't know if you have noticed or not, but when you pull up a pack, it no longer says ultralights and it no longer says lights; it just has the color on there. You have to look carefully, because you don't see it normally. The next time you see a cigarette pack, notice that. It is actually pretty cool.

We have a number of things coming up. April 2012, we have to establish the list of harmful and potentially harmful constituents. Our list will actually come out earlier than that, but one of the major challenges to that is, it has to be delivered to the public in a way that is not misleading.

Just think about going to your neighbors who are not scientists and explaining to them what benzene is, and the differences between benzene or toluene levels; it is very hard to

understand. We are working very hard on trying to figure out how to portray that to the public in ways they will understand.

By April 2012, so in about a year and a half or so, we are going to have to come out with recommendations for modified risk products.

October 2012, is the target date to revise and strengthen the warning labels for cigarettes. This is when the pictures will come out on the packages.

The Office of Science of the Center identifies, develops and applies the science that informs and supports the regulation of tobacco products in a manner that will have the greatest impact on improving public health. So everything we are trying to do is a focus on public health. It is very easy to get caught up in the deadlines and the statute, and jumping through the hoops. We are constantly trying to remind ourselves that we are about public health. I have found it very challenging. All of us find it challenging, because there are deadlines that are right in front of us. But that is our thing. We are focusing and constantly trying to remind ourselves about the importance of public health. We are broken up into four areas in the Office of Science: product science, individual risk, population harm and regulatory science and management. I came up with these names. I came up with these names because I didn't want to talk about chemistry and toxicology and social science. I wanted to emphasize what we were really

doing. What we are really doing is looking at individual risk and we are looking at population harm, because that is the way I view tobacco products. They are risky and they are harmful, and we are trying to address those things. We have a group that does regulatory science and management, which will organize everything and make everything go through.

Our primary task is supporting our advisory committee, the Tobacco Products Scientific Advisory Committee. We process and interpret the information that is obtained from the tobacco industry. That is a very major effort and something that is very overwhelming to us at this point.

We provide expertise for the scientific basis of regulation. We are in the process of writing our regulations and our guidance, and we provide the science to the regulatory folks on how to exactly do that.

We identify gaps in knowledge and perform research to fill those gaps. We don't allow the science to remain static, which is very important. We continue to push it. We push it forward, and we fill in the gaps we don't know so we can have the best science to address the problems we are trying to address.

We provide scientific input in the development of guidance and regulations, and we also have the job of reviewing all the tobacco product submissions for reporting premarket review, substantial equivalence and modified risk in our office.

All of that falls within my office. My office has gone from 12 people up to 23 people, and we are climbing steadily.

We have a wide variety of scientific expertise. One of the things I am trying to do is reach out and get scientific expertise over a wide range of people. We are talking about chemistry, the chemistry of tobacco products, and physics, how the particles are made, engineering of the product, toxicology and physiology, risk assessment, biomarkers, and clinical trials. We also have to understand genetics.

We were talking earlier at lunch about the difference in genetics between people. They metabolize the product constituents differently. Abuse liability, surveillance, psychology, all the way around to advertising and economics is different for everyone. I guess there are certain parts of the FDA that does deal with advertising and labeling, such as over-the-counter drugs deals . We have to consider those things too, because they have a major impact on population health.

This is us. This is the entire Center for Tobacco Products as of June last year. I had been there for about four days. We are continuing to grow, and we are continuing to develop. We are bringing in a lot of people. The people here are very excited about what they do. Most of the people are here in the Center because they feel very, very strongly about the

mission. It is a very exciting group to be around and to work with.

This is our contact information for anyone who would like to contact us. I would be glad to answer questions.

DR. AFSHARI: We will open it up with Diana.

DR. DOW-EDWARDS: Coming from a substance abuse perspective, I sense your interest is in lowering the nicotine content in cigarettes. Since the nicotine content, at least according to my limited knowledge, is the substance that is the abuse substance, what would be the rationale for lowering nicotine if individuals would just smoke more and then be exposed to relatively greater coal tars and so forth?

DR. ASHLEY: There are two theories. I'm not, at this point, committed to lowering nicotine. I am pretty committed to lowering the addiction. Nicotine is probably the main actor, but there actually may be other actors. We have talked to people who have left the tobacco industry and they say they could take all the nicotine out and keep it just as addictive. But that is a different question.

There are two trains of thought. One train of thought is to lower the nicotine below a threshold and basically no one will become addicted to products anymore. We save the next generation. These kids would start smoking it, they wouldn't

become addicted, and they would throw it away. That is one approach.

The other approach is to raise the nicotine up. Let's go through the roof with it, so you take one puff and that is all you need, so you don't take any puffs, you lower the toxins. We need to do the research to figure out which is the best.

Currently, the research I have looked at says that if you lower the nicotine in certain ways, there is some compensation, but not much. If you take the nicotine and cut it in half, after awhile people just can't suck on that thing enough to get all the nicotine they need. They will lower their exposure.

One of the questions we are dealing with in the research is how to lower exposure. Do we have it at a certain level and tomorrow drop it down to ten percent, or do we take it to 99 and 98 and 97, and slowly drop it down? We don't know how people will react. If you do it slowly, people won't even notice. They are used to how they smoke the cigarette and they won't even adjust the way they smoke until they get to the point where they say, this thing doesn't do it anymore, I'm just going to quit, and walk away from it.

So that is the research we need to do to find out the strategy of how much people will compensate. But the research right now says they don't compensate as much as we thought. There

are ways to design the cigarette, which would be part of the product standards, to prevent people from being able to compensate. Taking the ventilation holes may be one of them, because that is a major way people compensate. They can cover the holes, they can open up the holes, and things like that.

So that is clearly a major issue we are working on, and we are trying to do research in that very question.

PARTICIPANT: I have seen a product advertised called e-cigarettes. It is a plastic thing.

DR. ASHLEY: The drug delivery. Is anybody here from CDER? E-cigarettes are drug delivery devices, so it falls to CDER. Again, I look at this as a claims issue. They are making clear drug claims with those things, so they are drug delivery devices.

PARTICIPANT: (Comments off mike.)

DR. ASHLEY: That is a really good question. It is a very interesting question, and honestly one I have not spent much time thinking of.

I think we have multiple solutions to obesity. There are many different pathways we can go down to try to address obesity besides giving them something that is going to kill them. I guess we could end the epidemic of obesity by just giving them poison or something. So I don't think it is a smart thing to try

to solve one problem by giving them another problem. I think we have to come up with some solutions for both of them.

PARTICIPANT: (Comments off mike.)

DR. ASHLEY: If they need hand-to-mouth, let's give them something. They can eat rice cakes. Let's give them something else if they need the hand-to-mouth to prevent them from eating fast food; there are solutions to that. If they simply need nicotine, there are approved drug delivery means of getting the nicotine they need. I don't know if you need it for losing weight, that probably isn't the indication, but there are other ways to solve the weight-obesity problem besides killing them.

PARTICIPANT: I just have to address this drug delivery device, since you have mentioned it so many times. There was evidence during the Kessler era that the companies were titrating to addiction, and that the average cigarette was more constant than the USP reference standard. I think that is what promoted some of this.

What I am curious about is the mechanisms for your user fees. Are they renewed every year by Congress? What are they based on, and what kind of a budget do you have?

DR. ASHLEY: The user fees are actually specified by statute. So user fees in the first year were approximately $80 million, the second year was $240 million, the third year was $420

million and it is specified by statute out to 12 years, rising to about $800 million at the ten or 12-year mark.

People often ask me the question, and we have actually been accused in the news of trying to perpetuate tobacco use so we can keep the money coming in. But it is not based on the number of cigarettes sold. If we can get people to stop using cigarettes, their last pack of cigarettes is going to cost $800 million. That is fine with me.

So the amount of money is in the statute. If we can reduce it down, that just means every pack costs that much more.

PARTICIPANT: One last comment. I think that Kessler was responsible for initiating the carding of kids who were under the age of 18. It was shown that if kids don't smoke up to that point, they probably won't at all. I think it has already saved hundreds of thousands of lives.

DR. ASHLEY: Absolutely. For those of you who deal with kids, one of the hardest things is to tell kids not to do something. If a bunch of these old adults are telling me not to do it, it must be really cool, and so I am going to start. It is about message delivery.

Philip Morris and the tobacco industry have come out with a lot of these anti-youth programs that have raised youth use of tobacco. It is the way they phrase it.

So communication is probably our toughest problem. We need to figure out how to communicate things so it is not misunderstood and it is not abused or taken in the wrong way, so we can get out the messages to help the problem instead of hurt the problem.

DR. MILLER: Have you thought about how you are going to attack these research problems? Are you considering having a clinical research center in the Center of Tobacco? Or are you going to have contractors? Are you going to use academic settings? Are the cigarette companies going to be responsible for the research? Have you thought about how that will work?

DR. ASHLEY: Most of the answers to those questions is yes, one of those answers is no. We are definitely working with academic institutions. We are already doing that. We are working with NIH. We are working with CDC. We are hopeful to work with the National Center for Toxicological Research. We are hoping to work with other parts of FDA. That is one of my goals.

We are not working with the tobacco industry. When the law was passed, they got out of the research business. Philip Morris had a huge facility in Richmond, Virginia at their main center which, as soon as it became clear that the bill was going to pass, they shut down and took all of that overseas because they knew they didn't have to deliver the documents if it wasn't in Richmond.

We have lots of people calling us from there asking for jobs, which I don’t know how to address. That is another issue completely. Right now, we are looking at NIH as a great mechanism for getting research out. We have been talking to them. We are working with CDC a lot to do research for us. We are hoping to work with a lot of FDA to do research.

Our approach right now is not to build our own clinical centers or our own laboratories. We are working with ORA to do some work. Eventually we may; give us ten years and that may change. Right now we have enough problems without having to build laboratories. Since there are laboratories out there, we want to use those instead of trying to duplicate what is already accessible to us. We have plenty of problems.

PARTICIPANT: Just as a follow-up, I imagine if someone wants to collaborate you have to pay for that? How is that working? Is it a problem?

DR. ASHLEY: I spent 27 years at CDC, and I talked to lawyers probably five times over that 27 years. Generally, I talk to a lawyer probably five times a day in this position.

One of the words we can't use is the word “collaborate”. We don't collaborate with anybody, because that means the money is mixing and things like that. So there are certain things we do. We are definitely going to work with others. We have funds we can use to sponsor research. It has to be specifically research we

want to have done and research that meets the requirements in the statute. So that is no problem.

We can, for example, give money to CDC to do particular research we want to do. If CDC was going to do it already, we can't give them that money. But if it is something we want them to do, that is different -- I'm saying this because we have just been through two months of haggling with the Office of Chief Counsel on this. If we want them to do it and they were not going to do it anyway, then yes, we can give them money. We are doing the same thing with NIH. There are certain projects NIH would not be doing otherwise so then we can support them completely.

You also have to make sure the money is clean. The easiest thing is for us to support it completely and just not our money together. We can't put our money together. It has to be clean and distinct about what we are paying for and what the other organization is paying for.

PARTICIPANT: (Comments off mike.)

DR. ASHLEY: We have a research plan we developed. It is very long and complete. I would be glad to sit down with you. I am hoping to sit down with you guys and talk about specifics, so let's begin to work on things.

I have already taken a lot of notes this morning on things I can see clearly, things we need to do that you guys

already have the capabilities of doing so I am very interested in working with you.

So yes, I have a research list laid out already. I have some new ideas from this morning after hearing some of the things today.

PARTICIPANT: (Comments off mike.)

DR. ASHLEY: There seems to be a very clear tie between raising the price and the number of packs sold. In the United States, the number of packs sold is dropping regularly. You saw the curve where it went down and flattened out. Number of packs sold is continuing to drop down as the price goes up.

One of a couple of things is happening. Prevalence is not changing. The number of smokers is staying the same, but the number of packs sold is going down. More than likely, they are smoking the cigarettes harder. Instead of taking three puffs on it, they are smoking it all the way down. We don't see any decrease in nicotine levels. They are still getting the same amount of nicotine, but they are getting more nicotine out of every cigarette.

Taxes serve to drive the sales of cigarettes down, but you can only go so far. If taxes continue to go up, eventually people will not be able to get enough out of each cigarette-- you can only get so much nicotine out of a cigarette, there is a limit. If we can get the prices high enough, it will drive the

exposure down. But we still have a ways to go with that. It is clearly decreasing the sales of cigarettes.

PARTICIPANT: Since these are user fees technically, are they appropriated funds?

DR. ASHLEY: Our user fees every year have to be appropriated, yes. But right now unless they change the bill and redo the bill, they don't have a choice about how it is appropriated. It isn't coming out of the budget.

PARTICIPANT: Congress sets the limit of what you can get from the industry. The reason why I ask is, having monies go from one agency to another, is really not the intention of Congress to have extramural money go intramural, and across and so on. So exactly what it is has some interesting implications, I think.

DR. ASHLEY: We have done interagency agreements, and we will continue to do interagency agreements. We can continue to use our funds.

The bill actually says specifically that we will work with other parts of the government to do our job. So there are words in there that says we have to do that, which we are happy with.

PARTICIPANT: The Center itself where all those people are is where?

DR. ASHLEY: The Center is in Rockville, Maryland. It is actually North Rockville. It is really Gaithersburg, on Corporate Boulevard.

It is a facility that has been used by two or three different centers in FDA over the years. I think the last group there was a CDRH group. I think there is a CDER group there at one time. Right now it is just an office building relatively close to the Shady Grove Station, on the other side of 270.

PARTICIPANT: So $80 million is one and a half times the total budget for the NCTR this year. Can you spend it all? Is it physically possible? I have some ideas.

DR. ASHLEY: As we are gearing up, that is a challenge. Once we get completely operational it will not be a challenge. When we get to the point where we are fully functional, we will not have enough money to do our job.

Right now we have money and we are very interested in using that money to move some things forward. Now is a golden opportunity for us to do some of the research we need to put product standards in place years from now. If we want a product standard around nicotine reduction, right now we have the money to pay for the research to get that done so we will be ready for that product standard.

So doing the research is top on my list. We have the funds to do that now.

DR. HINES: Several years ago I was in the Sao Paulo Airport. Based upon signage, I would have sworn it was the Lucky Strike Airport. Do you have any authority whatsoever to regulate the offshore use or exporting of this kind of technology?

DR. ASHLEY: Absolutely not. The tobacco industry can do anything they want to if they are selling it overseas. Now, if they are bringing stuff into the country, we have authority over it. But this is just a domestic bill.

I do know the folks in Brazil. In my role at CDC, I worked with the folks in Brazil for years on their tobacco regulatory activities. That was a different job, different place.

PARTICIPANT: First of all, let me thank you for coming here and delivering this very interesting overview, and also for being willing to sit down and talk about some possible, not collaborations, but interactions.

Two quick questions. How did we reach the 12 percent goal, which I saw in some of your initial slides? How did that number come about, just out of curiosity?

DR. ASHLEY: It is a Healthy People 2010 goal. I think what happens is, HHS gets together and they ask what the aspirational goal is. Generally those things are pretty aspirational. They are not what we think will probably happen. They are thinking what we would like to happen, what would we really push for, and they get together.

That is a pretty tough goal to meet. But back in 2000, they said by 2010 this is what we would like to happen. We would like to have it down to 12 percent. I'm not going to say that was unrealistic, but it was definitely aspirational. Then we use that goal as a means of pushing Congress pushing and pushing our research agenda because the only way we can do this is to do these things.

So it is an HHS process, the Healthy People process.

PARTICIPANT: The second thing is that the 12 or 13 percent is about where smoking during pregnancy is. It brings up a very interesting question. FDA is in a quandary of trying to reduce smoking during pregnancy and having clinicians suggesting using the patch, which is nicotine.

Then you can get to a spinoff on Stephen's question, that nicotine has its own set of issues associated with it, especially during development. Some feel as though it is a teratogen. So how do you deal with that epigenetic quotient that may be associated with nicotine and how we deal with it in terms of the patch versus traditional nicotine exposure from the cigarette? That is something that FDA is right in the middle of when it comes to the over-the-counter application of the patch versus your obligation within the tobacco products area.

DR. ASHLEY: It is a very tough question, because there are a lot of factors. I have not come up with a good equation yet

that says how you plug all these things in to figure out what the ultimate population harm is from all the options.

That is a very interesting, possible thing for someone to think about very carefully, because clearly nicotine is not benign. Nicotine is not just addictive; nicotine does have its own adverse health effects. Otherwise it wouldn't be a pesticide.

I am thinking about everyone in this room. If you had a person who is smoking cigarettes and you could get them to stop smoking cigarettes, or even move to smokeless tobacco, that would be great. It would be better if you knew a smokeless tobacco user and you could get them to move to the patch. If you know a person who is using the patch, it would be great to get them to quit all the way.

So there are different levels of toxicity for the individual. But the problem is, we are not just looking at individual risk, we are looking at population harm. So we have to calculate the impact of each of those things on non-users and everything else. So the overall harm is a very tough equation. I've not seen anybody who has come up with a really good mathematical equation to plug all the numbers in and come up with that answer.

I just know that what we need to do is try to reduce that overall harm without getting more people addicted to the

product. I know that is not answering your question, but it was a way for me to talk without actually answering your question.

Agenda Item: Presentation and Discussion of NCTR Strategic Focus and Future Direction

DR. SLIKKER: Again I wanted to thank David for a great presentation. It really helped us get oriented to the role of tobacco products in FDA.

I want to spend a little time talking about our strategic plan. This document is in your packet . This plan is really essential for NCTR, because it outlines a five-year look at where we want to be in the future. It is generated from the scientists at NCTR, coupled with input from the other centers of FDA, and it is updated on a yearly basis. I want to spend a little bit of time going over this so we can hopefully use this plan more successfully in the future, and we can get more input on this plan from our science advisory board and from the other centers of FDA.

We have already been talking with some of the group here about how to get an enhanced review of this plan on a yearly basis from the other centers, and how to involve more people in this process. So, I want to go over that and look at the strengths of this plan, and also get your input on the value of this plan and how we can improve it.

What we are talking about is supporting the FDA mission. These are some of the ingredients that are in our plan. It, of course, involves the innovative, interdisciplinary research we do here at NCTR. It also involves the idea of improving the technology, and using the improved technology to develop new approaches to safety assessment. It also includes the idea of interacting with others throughout the world and throughout FDA to solve these kinds of problems and bring teams of people together. This was shown in the microarray quality control one, two and now moving toward three, for example, to look at bioinformatic approaches to solve issues within the FDA area of concern.

Then finally, there is the idea of international harmonization, globalization, and the idea of training individuals throughout the world to improve regulatory science. So those are really the fundamentals of our plan.

We have three main goals within that. The goals here are the science goals. The improvement of this plan over the previous year's plan is that we have incorporated all the science into one goal. This is now plan number five for us. That was not to diminish the importance of science, which is our main feature here, but to make the document more readable.

You have already had the opportunity from each one of the division directors plus others from these cross-cutting functional groups, so I am not going to spend a lot of time with

science, except to give you some idea of the breadth of that area, and spend more time on goals two and three, which have to do with communications, recruitment and training. These are some of the newer areas of emphasis we think are so critical to moving NCTR and the agency forward. That is what I am going to do in a relatively short period of time.

The idea is that all of these overlap. You are not going to have a product unless you have the science goal, but you need the communications, recruitment and training in order to build and let people know about the role of science.

Looking at the strategic plan for goal number one for science, you can see that it is broken down into objectives and strategies reached from those objectives. This is the approach we use throughout the plan.

The idea is to have an objective that is something accomplishable and within the time frame we are speaking of, and to develop a strategy of how we are going to do it. In this case, you can see the integrated safety assessment is objective 1.1. Underneath that, we may have one major strategy and many subgroups. You see here objective 1.2 and 1.3, for example.

How this breaks down is that under goal number one, we are at 1.1. You can look at the objective, which is an integrated safety assessment. You can look at the strategies associated with that, and then the important part, the outcome measures and the

time frame associated with that. The idea is to get outcomes on the plan so one knows what they are trying to accomplish, and the time frame in which we want to see that done.

This particular one involves these comprehensive toxicological evaluations Paul Howard and others talked about in terms of the work we are doing in conjunction with the National Toxicology Program, or with other groups, including other centers, as well as NICHD and EPA. But a whole host of compounds are being evaluated, as Paul spoke of, as did Fred Beland, such as bitter orange, Bisphenol A, et cetera.

This is how we get the content into the strategic document and how we talk about the objective, the strategy and then the outcome measure we want to accomplish.

Another example of that within the science side is 1.2. We are talking about advancement of scientific approaches and tools. This gets into the kinds of things Jim Kaput was talking about in terms of the methods to generate data for the individual. It is also important when it comes to new bioinformatic tools as well as new biomarker development. So under that you have the objective, the strategy that goes with it, and the outcome you are looking for and novel biomarkers to be developed. This could be everything from the imaging biomarkers Merle Paule will talk about more tomorrow, or it could be some of the biomarkers we heard about today, dealing with some of the bioinformatic tools or other

kinds of omic approaches that were nicely spelled out. So this is the way the plan is developed.

I want to leave the science area and spend time on the other two goals and develop those a bit further.

Here is the third area under the science side. Now let's go to goal number two. Goal number two is about the internal and external communications. It is really important for FDA and for NCTR, in particular, to be able to communicate its activities within the agency and outside the agency, and around the world, for that matter.

We looked at a number of different possibilities to do this. Of course, we have better tools than we had before, such as the Web 2.0 tools that are now available. The idea of reaching outside the U.S. to other countries is more available using various kinds of newer Internet approaches, and we want to be able to link up and talk with other folks within other government agencies, within academic facilities and within industry.

So to do this, we also wanted to develop and strengthen our communications with the other centers. We are doing this through a number of means that will be elaborated in these next few slides. Communication is really important to accomplish the full goal of NCTR.

Here is goal number two outlined in terms of the three major objectives and the strategies that go along with those.

Some of it, on objective 2.1, for example, looks at some of the tools you can use to develop a better Internet association and web type tools, such as 2.0. In doing this, we also want to be able to have greater communication with our colleagues at White Oak, as White Oak becomes one of the central places for FDA in Washington and more and more groups are being able to move there, including our own office that Peggy Miller occupies along with Kim and others. We want to be able to broadcast their webcasts so we can have seminars and exchange information. We can see what they are doing, have their seminar, ask questions and vice versa. So that is one area we want to expand.

In the 2.2, it has more to do with how we deal with the outside media. We are getting more and more requests for information about our studies and about the progress we are making, so we need to be able to do this.

One of the goals is to get better communication strategies for NCTR. To do this, we are developing a committee as well as hiring a new individual to help with this. So those are some of the areas we are dealing with in strategies.

The 2.3 deals with education about the tools that are available. We find it very interesting, just as mentioned by David, that there are a lot of tools and techniques here that maybe he wasn't aware of before, and now he knows more. But we

want to be able to reach out to others within FDA, and that is one way to make those available as well.

Under 2.1, you can see the objective, the strategy and some of the outcomes we hope to achieve. This is in the time frame from 2010 to 2012. We want to recruit a communications specialist. This is going to be a high level individual. We already have the recruitment in progress. We hope to be able to hire somebody in the next several months. But the idea is to improve our communications between our staff here on this campus, in addition to the communications to others throughout FDA and to outside media outlets where appropriate.

Also, we have already formed a communications council. This is a group of individuals here on this campus to help us enhance this communication possibility. The new communications specialist will be one of the key members of that new group.

Also, creating profiles of NCTR researchers and expertise, making that freely available to the rest of FDA, and to establish a series of seminars that can be implemented at White Oak is also part of the communication goal. The idea is using webcasting to be able to give seminars here that can be seen at White Oak and vice versa. So those are some of the outcome measures we are looking for to support objective 2.1 and goal two.

You can go through 2.2 in the same fashion. Some of the key outcomes we hope to have here are to improve our website

location. A lot has already been done. We have quality people on the staff who have been working toward this goal already, but we think it will be enhanced once we get our communication expert here and coordinate that across NCTR and into the other centers.

Objective 2.3 deals more with improved communications within the center and making more things available online. We will be moving toward that. We have already conducted questionnaires and surveyed individuals on this campus to try to find out what the greatest needs are in the communication area, how we can improve them, and then how to establish strategies to implement them.

One of the things it includes is the standardization of our presentations. You probably have noticed, perhaps, that we are using a slide format for almost every presentation you have seen today. The idea is to have this as more of a marketing device when we go out to others across the U.S. and outside of the U.S.

Let me leave the communications area, which we think is an important area, and move to the third area I want to cover. That is the recruitment and retention of experts within the area of regulatory sciences. We feel this is really an important area.

NCTR for years has been training scientists, both as graduate students and as postdoctoral fellows. We have usually had a cadre of 30 or 40 postdoctoral fellows there at any one time

over the last 15 or 20 years, but now this has been greatly expanded. The number of postdoctoral fellows is now reaching up toward 80 or 90 in total.

This is really important to us, because we think we can make a significant difference in the training of regulatory science throughout the U.S., and this impacts other countries as well.

One of the areas that have helped us with this expansion has been the FDA fellowship program. These are individuals, usually six or seven per center, who have been selected. We are now in the third year of that. Currently, we have around 20 or 21 of these fellows on our campus. But, we also have staff fellows and ORISE.

ORISE is a program that allows us to hire individuals through a contract mechanism through associated universities. This means they do not have to be government employees to work here. This can help a lot, especially for some of our foreign nationals.

Through those mechanisms, we have been able to add individuals to this whole area of regulatory science for training. But there are other areas of training we want to hit as well. The question is how do we get well-trained, highly-motivated scientists to work within the FDA, and for those who don't find a home here after their two or three years of training, they may go

to other parts of the government or to industry. But in every case, they are well-trained. They are out there making important regulatory decisions, and hopefully they are making decisions that are consistent with FDA values. They are doing this, both, in the United States, and maybe just as importantly, they are doing it in foreign countries as well.

Here is how number three breaks down in terms of recruitment and training. You can look at the objectives across there, 3.1 through 3.3. One of the goals is to develop and implement a strategic plan for succession planning, which we have that document now. This is the version of our plan for 2010 to 2014, so we have an idea about what our needs are going to be for NCTR in the future.

This came about by looking at mainly the management jobs and the leadership jobs throughout NCTR. This plan will help us understand what we have available. There are some important statistics here. One thing is that about 100 percent of the senior management of NCTR is in the retirement age zone.

This is fundamental; it has to be understood. About 30 percent of all of our middle managers are within the retirement age zone. So we are in a situation where we need to be looking for new ways of bringing individuals into NCTR.

This is not too surprising. This is happening throughout the toxicology environment. The reason is that it was

about 30 years ago that a lot of the legislative packages were passed to bring toxicology into the forefront. When that happened, a lot of toxicologists were hired in university settings; they were hired within government institutions, the EPA, and the FDA, for example. Now within all of those organizations, the people are getting ready for retirement. That doesn't mean they will right away. Many individuals are going to stay for many more years, but the point is that it is possible for them to retire. We need to be dealing with that issue and training people appropriately. So that is part of the objective with goal number three.

We want to have these programs where we can explore these partnerships to support regulatory research and training, and to do it in a quality way. We want to do this by working with other centers of FDA, who, oftentimes, will reach out to other groups as well.

Some of the programs we have developed under 3.3, in particular, and some of the strategies, are to deal with these kinds of programs where we bring in scientists from other parts of FDA to train at NCTR. We found this to be very rewarding. A lot of times these are reviewers who will have a chance to learn some of the modern technology because they are very much in the groove of doing their review cycle work. So we can bring them here for two or three days. We can show them how you might be able to do a

new kind of assay, maybe genetic toxicity testing, maybe a bioinformatic tool or maybe a new omics approach.

They take that information back and use it in a review process. It trains them in such a way that they are then able to deal with the uncertainties of some of these newer technologies, and they will interpret them for FDA. So, we find this to be very rewarding.

One thing we want for the future is to reverse this process and have some of our staff go and work at the other centers of FDA. We are already thinking about some possible examples, maybe something to do with safety assessment or maybe something in the area of the nanotechnology, but we are going to find areas where this training can go in the other direction as well.

Let me give you a bit more detail on this. Under goal number three, objective 3.1, we have some outcome measures. One of the first things we want to do is find out what our needs are going to be in the next ten or so years. It is painfully obvious that we do have some issues to deal with in terms of replacing some of the staff that is eligible for retirement. So, that part has been accomplished.

Under this one, 3.2, some of the outcome measures involve these workshops. We brought in scientists and reviewers from other centers to train with us for periods of two or three

days, and have put together small workshops under the STEP program operated by Peggy Miller. It’s usually five or six people from one center and five or six from another. We found this to be very successful.

We have done some of these with CBER with Carolyn Wilson's group and found this to be very productive. We are planning one in the future on nanotechnology with CDRH and perhaps other centers as well. This is something we have been doing more and more, two or three a year, and we hope to be able to continue this. Also, we have been able to get help from some of the other centers to help fund this travel.

Understanding the needs and basic fundamentals of stem cell research within the FDA is important when bringing these people together in small groups like the one on stem cells Jim Kaput put together.

Then for 3.3, outcome measures which we see from 2010 to 2014 have to do with the idea of gaining experience with certain new technologies, and also about this idea of sabbaticals. It is not unusual for FDA employees to have a chance to do a sabbatical. It hasn't been used as much recently as it was ten or 15 years ago, but a sabbatical at some key times in one's development can be significant. We are thinking about this opportunity to have people come here and do a sabbatical. We have had plenty of those from academic settings, but we would also like to have scientists

from NCTR go out and do sabbaticals in academic centers or within other parts of FDA.

Let me leave that then to talk a little bit about communications and about planning for the future.

I want to turn to the last part of our presentation and talk about regulatory science, because this is such a key issue. We all know about Dr. Hamburg's support and interest in this area. We also know there have now been grants that have been jointly funded by FDA and NIH. The money started out at approximately seven million and went up to nine million to fund the first round of studies. There were four studies that were funded.

There was talk that approximately twice that many were worth funding. I think this program is considered for expansion next year. Here is Dr. Francis Collins and Dr. Hamburg coming together, putting in funds mutually to support this area of regulatory science. It really is a step forward. It means the governmental agencies are going to have help in moving regulatory science forward in the future.

We all know about regulatory science. It is a diverse set of skills and capabilities. But certainly a lot of it is this bridged idea between the clinical, basic research and marketing of products, and how you speed up that particular pipeline. It also has to do with population, clinical manufacturing, and behavioral science. It is really broadly based.

The other thing about it is that it enables products to be moved through the pipeline faster, which gets us to the critical path idea. We are very happy to have Leonard Sacks here to talk more about that tomorrow afternoon and other times.

We are moving this area forward. One part of this is collaboration and outreach with others. This can be traded operations through universities and through various kinds of industry, and also interagency agreements with other government agencies.

Let me turn finally to training programs. I have been talking about training programs, but I want to list them here to show you how important we think this is to the future of regulatory science and to the future of NCTR and FDA.

We have a number of training programs. We talked about postdoctoral training programs, the FDA fellows, the ORISE fellows who are very handy because they don't require a U.S. passport, and FDA staff fellows who do. All three of those are available for postdoctoral fellowship training.

Then there is the NCTR STEP program I mentioned operated by Peggy Miller. This program trains individuals within the FDA. We also have our visiting science program where we have sabbaticals come in from various universities or other parts of FDA and other government agencies, and the summer sabbatical program, which is very good for university professors.

Then we also have an undergraduate program during the summer where we train somewhere between 15 and 20 or so undergraduates, and hope to get them interested in science so they will stay.

International capacity building is a relatively new area for us. We have always trained a lot of postdoctoral fellows from foreign countries, but this time we are linking hands with a lot of our groups from the overseas operation, Mac Lumpkin's group, in international affairs.

What we are able to do is link up with students who are in these various countries who want to have this advanced training. We are also doing this from countries like Africa, South America, and a lot of Asian countries. This has been an expansion area for us just in the last year or two.

The idea is producing global training and global standards to promote global health and safety. We think that if we can train these individuals and they return back to their home country, they will take that training expertise with them and have it available to make good decisions there. It is a great linkage between the FDA offices that are in these various countries and the home country to train those individuals. In many cases, here at NCTR, we send our experts there to train them in their home environment. So, either way it works out for training individuals for the new global outreach of the FDA.

With that, I think I will close by summarizing what I think our strategic plan is doing for us. I won't cover all of these, but I just want to mention a few of them. Certainly, the idea is to find a way to get more information to the FDA reviewers. We would like to have more information available on their desktop using bioinformatic tools so they can make decisions more rapidly and with better data sets.

We also want to be able to talk about these new standards and guidelines. Many of these guidelines are developed hand in hand with individuals at various other regulatory centers, and we want to continue to do that. We just recently linked up with the folks within CDRH that have been doing the genetic testing and have someone on that committee.

Martha Moore and her colleagues have been working with others to look at the genetic toxicity testing guidelines, and Weida Tong and others, including Donna and Leming, have been working on those for bioinformatic tools as well as for certain guidance on omics technology. We think we can have an impact on that guidance document development in the future.

Also, I am pleased with the idea of just having this cross training of scientists, and having the ability to train individuals who will support regulatory science throughout the FDA and throughout the world, for that matter.

And the idea that we can ultimately use NCTR technology to support FDA centers in making rapid and accurate safety assessment decisions works toward these goals. We want to continue to do that and build on that. One way to do that is through meetings like we are having today.

With that, I just want to close by saying that our job here at NCTR is to bring these groups together, both individuals from the various centers, individuals from academic centers, industry through IAGs and CREDAs, and to interact with our scientists here to promote regulatory science and the application of that for FDA-regulated products.

With that, I will close and be happy to try to answer any questions you may have.

PARTICIPANT: Bill, at the beginning you commented that you would like to get some more input as you put this strategic document in place. I was wondering if you could give us a little background on how you have gotten to the current document, and what is the current process.

DR. SLIKKER: As I mentioned, we are now in our fifth issue of this. It comes out each year.

The way to go about doing that is having go-aways that are usually late in the year, November to December, and then in January of each year, get the NCTR scientists together to discuss how to improve the document. Sometimes that means restructuring

so it makes more sense and is more succinct. As you know, we got it down to about 15 pages.

A lot of the back portion of this is a glossary of terms, and several pages are an appendix. It links the Health and Human Services goals to the FDA goals and then to the NCTR goals. We are putting together a stream between the Department goals, FDA goals and NCTR goals.

So there really are only about 12 pages of content now, which is much more manageable than ever before.

After that first round of improvements, it moves out to the various other centers of FDA. We start with the center director. They usually pass it down to others, get input, and then it comes back to us. We use that to improve the document. All of that is incorporated into the version that is distributed FDA-wide and put on our website, and that is also in your packet.

That cycle will start again month after next, and then we will begin the whole cycle again. Does that help a little bit?

PARTICIPANT: Yes, it does, thank you.

DR. HINES: Bill, let me ask this. Have you laid projects to rest? Have you evaluated them and said, we have achieved this goal and therefore it has gone off the plan? Has that happened? Do you have a regular means of doing that, evaluating when you are within a particular project on a particular goal and moving forward?

DR. SLIKKER: That question is kind of complex because we have our goals in here that are updated on an annual basis, and then we also have about 200 active protocols at any one time. So are you asking more about these?

DR. HINES: Yes.

DR. SLIKKER: Hopefully, you noticed the outcome measures, and set time lines. Some of them were in 2010, and the idea was a form of communications concept, not too difficult. We were able to do that this year. In 2011, we hope to hire the communications expert. That is going to be done, so we can check that off.

So yes, we can definitely check off some of these goals. Those other ones like training, for example, will continue through training mode for quite some time. We may come up with new mechanisms like the small group interactions, or like sending one of our scientists to visit with another center and work with them for several days or several weeks.

That is something we are trying for the future. If it works out, then we will keep it longer. Otherwise it will go off the books.

DR. HINES: The point of my question really is the importance of evaluation and self-evaluation, as to where you are with the planning and where it needs to go.

DR. SLIKKER: Exactly.

DR. HINES : And making sure that it is in place.

DR. SLIKKER: I think one example of that, Ron, is that this document went from 25 pages down to 15, because we found a more succinct way of writing it up, and to focus on some new ideas as well as the science ideas that are so central to it.

So yes, we are always trying to improve how this looks. We are asking for input from the other centers to do the same thing. I appreciate that question.

DR. BAKER: A lot of these outcomes are qualitative in nature or they are somewhat new. Did you guys discuss putting some kind of quantitative metric on some of these?

DR. SLIKKER: That is a very good and important thing to do. In fact, you may be aware that we now have FDA Track, which is focusing on those quantitative measures that are for each Center to have this kind of information available online.

We are moving more and more to quantitative outcome measures. As you can imagine, sometimes it is difficult when you talk about outcomes and research projects. You can say we are going to have a paper by a certain time, but the outcome of that paper a year in advance is hard to predict. So we have to be a little bit qualitative about this, but we are trying to move toward more quantitative goals. You are absolutely right in that. Some of them are straightforward; some of them are more difficult

to nail down. But it is something we are moving toward. Does that answer your question? Is that what you wanted?

DR. BAKER: It is kind of hard to do that. Like you say, if you are going to impact three out of four programs, you sometimes have to do descriptive and not exact measures, But it's a way to have some numbers.

DR. SLIKKER: Yes, exactly. That is why there are some numbers in here in terms of how many of these small group interactions we want to have, and how many of the step exchanges we want to have. We can put that kind of thing in there as a target goal, but we also have to consider that there are going to be funding issues. Oftentimes you have to wait for that to unfold, which could be months after you actually come up with a plan.

But you are absolutely right; we try to be more quantitative when we can be.

DR. WATKINS: You mentioned the regulatory sciences center program. That is set up as a U-01, which is a cooperative, and generally has a heavy hand of the NIH staff in it. Is there going to be a combined FDA-NIH advisory committee for that?

DR. SLIKKER: Yes.

DR. WATKINS: Is the NCTR represented on that oversight committee for this U-01?

DR. SLIKKER: There is a coordinating council that is set up between scientists from NIH and FDA, and NCTR does have a seat on that council. We are going to meet here in the next week, in fact. The idea is to set some general guidelines for this.

But that council is not going to be making the decisions on the individual grants. That will be separate. But we will be talking about support of that program and how to best focus it to meet the needs of regulatory science. So it will be general guidance, but will not get down to the details and decision-making about grants. Does that help?

DR. WATKINS: Yes. I think I am a little bitter, because I applied for one and didn't get it.

DR. SLIKKER: Hey, don't worry about that. There were two from individuals from NCTR, and neither one of those did.

DR. WATKINS: It did strike me, looking at the titles of the grants that, with the exception of one that was designed for clinical trials, it wasn't obvious that they were in any way related to regulatory science as you defined it in that list. I certainly couldn't see a common thread there.

If this is really designed to be a new effort in providing the scientific underpinnings for judging risk and benefit and setting policies, then NCTR should have a prominent seat at that table, both deciding the directions and overseeing this.

DR. SPIELBERG: I don't think it is the first time you have tried to find a successful way to intervene with the review panels, and it won't be the last, either. But I don't see us intervening with this review panel.

However, I would like to see it strengthened. I would like to see more money in that category and more options, because we are talking about funding at somewhere between a five and ten percent level, which is quite low. So I think there is room for improvement in terms of funding in the future.

I think that having a large number of good proposals boosts the opportunity for more funding to be available next year. That is the hope.

DR. SPIELBERG: Bill, we are right now at the Science Board in the midst of the review of adverse event reporting at CDER. One thing that has come up repeatedly in the discussions of that external panel is a need for enhanced mechanistic approaches to toxicology.

The evaluation of Adverse Event's is difficult enough anyway, given their sources and given the sparse amount of information often provided by physicians, pharmacists, and increasingly, lawyers when there is a bandwagon underway. The issue of trying to focus efforts in a timely way in the interest of public health often is going to rely on biological

plausibility, but if it is something new, how could it be biologically plausible? We don't understand mechanisms.

One thing that has come up in the discussions is what role can NCTR play in this in real time, both in terms of providing a mechanistic basis for hypothesis generation, as well as on the preclinical side to better prepare preclinical development of drugs to understand what tensions exist to prepare clinicians with an open mind for being able to gather that information.

Is this a role that NCTR can take on now? Or is it just pie in the sky? From my point of view, having spent most of my career looking at patients in real time with adverse drug effects, we need it desperately, so where is it going to come from? Is NCTR going to be a place where it can provide this support. --

DR. SLIKKER: Stephen, you have defined a very important opportunity and a very important need. I don't mind sharing our story about the pediatric anesthetics with you. I think it fits in beautifully with this.

Here you have an issue, Joe Hanig is here and he is one of the prime movers of this within CDER, where you have a prime example of how animal studies can prepare the clinical researchers to provide the best kind of study design to answer the question in humans. You have the opportunity to show how animal data in now five different species have shown this developmental effect with

anesthetics for protracted periods of time, and that there are certain kinds of behavioral end points that can be monitored, and certain kinds of histological changes unlikely to be found in humans, but we are covering that by using non-invasive imaging to try to look at those same end points.

Now we know something about the window of sensitivity. We know something about the duration of exposure to produce these effects, and we know something about the end points we need to be looking for. All of that is available now to the clinical researcher to take and move forward to the next level. They are doing that. They are really listening.

I have been to several anesthesiology meetings now and others have as well. Last time we had an entire day just to talk about this topic. There is so much interest there. Now we are finding funding modes for them, including reaching out to the various kinds of FDA funding to get support for clinical studies to answer this question, but it is based on the animal research. I think we are doing exactly what you are saying, and we are doing it in ways from acrylamide to Bisphenol A to methylphenidate to the anesthetics to various kinds of dietary supplements to nanomaterials in the future. We are trying to determine what the plausible mechanisms are in the animal studies, what end points we need to be looking for, and to then apply that to designing, in

some cases, better clinical studies so you can get the answer in humans.

In some cases you are going to be making decisions solely on animal data, as you know. But oftentimes when it comes to therapeutics, you are going to need the human data to go with the animal data. We are there to support the kind of design you need in the new clinical study to make it successful.

DR. SPIELBERG: So you would not be unhappy with the argument that includes partners between NCTR and the Office of Surveillance and Epidemiology?

DR. SLIKKER: We would be very happy with that. I think Joe Hanig sitting here from CDER would say that there has been many, very positive interactions between CDER and NCTR in this regard.

DR. HANIG: I will talk about it later on, but I think the way in which NCTR has satisfied some of the most urgent needs of CDER from the research point of view is nothing short of spectacular. We hope that it just continues and gets better.

DR. SPIELBERG : We couldn't agree more. That is one of the things the panel has been looking at. Electronic records in this country are designed for billing, not for patient care, not for teaching, and certainly not for research. We really need to capture the clinical richness in a way that busy people can do it, and then provide people at a mechanistic level an appreciation for

the sum total of what goes on in a patient that can then lead to a hypothesis that comes from the basic side, feedback to the clinical side, and do it in real time because of the sense of urgency.

DR. AFSHARI: Bill, I had one comment in terms of the consideration of the training program, and an opportunity for NCTR. You spoke about some of the emerging technologies and platform, and the opportunity to educate folks from other countries in terms of some of the regulatory science. One of the things we hear is that, as you mentioned, the classic toxicologists are now reaching retirement age. A lot of those folks were trained with hands-on, animal dosing and in life-type experiments within the animals.

One of the things we are seeing now as graduate students emerge out of modern toxicology programs is that they are more molecular-focused, so we are losing an appreciation for some of what happens when you have that experience of working with animals directly, appreciating some of the background incidents, and the things that can happen during those experiments. A lot of people doing research in toxicology today look to the more seasoned cohorts to put the whole thing into perspective.

I think it is an interesting opportunity here at NCTR where you conduct so much in life and in animal work, and to think about continuing to keep that up as a strength with your training

programs and allowing the new toxicologists coming through to not only appreciate the molecular aspects, but the more physiological, whole animal aspects as well.

DR. SLIKKER: Cindy, I couldn't agree more. As you can probably figure out, NCTR is designed for those multidisciplinary approaches and for training individuals who may be involved in studies where you have a small number of animals or perhaps you are using an animal as its own control through imaging and other approaches, to very large studies where the study director role is very much emphasized and trained, complete with GLP or an opportunity for human use.

The training opportunities are diverse, and they are available to hopefully train that regulatory scientist for the future. I agree with you that many of the existing training programs are focused on hypothesis testing which is great but oftentimes relatively narrow.

The two or three years at NCTR for the postdoctoral training allows one to expand beyond that, include whole animal studies, which includes the mechanistic work that links them together using either biological models, pharmacokinetics or other approaches.

I think that is a role we can play, and we want to do that in the future.

DR. DOW-EDWARDS: I am very impressed with many aspects. I am questioning your move toward recruiting younger senior people or semi-senior people with an emphasis on training, and the apparent increase in training you have initiated. Where are you getting funds for this, if I might ask?

DR. SLIKKER: Training of the individuals in these programs?

DR. DOW-EDWARDS: That, and also the recruiting of additional younger, senior people.

DR. SLIKKER: Well, Diana, it is somewhat a zero sum game. As people retire, we are usually allowed to replace behind those. Oftentimes, that means we probably won't recruit someone who is in the same bracket as the person who is leaving.

There has been some expansion. Part of that is because Congress has recognized that if they want FDA to do all that it needs to do, we need a few more people to do it. Remember, all of FDA has about 12,000 people. That is smaller than some school district teacher populations in the Washington, D.C. area. It is a very small number of people to do the work that helps regulate about 25 percent of every dollar you spend.

I think Congress is saying we may need to add a few more people. NCTR is getting a small percentage of those from the grand total that is coming to the FDA. So there is some increase.

The student increase, these are mainly postdoctoral fellows and beyond. A lot of these FDA fellows have already been in industry or in academics or some other mode for two or three, or four or five years before they come to this program. So, some of them are already quite well-trained. But for those individuals, we are taking money out of the operating budget and using it to support these students to train them in this FDA fellowship program. All the centers are doing it, not just us alone.

So the idea is to put good money into training quality individuals, but take it to a new level with training that is more regulatory science-based. So it is difficult to find the funds, but we think it is so important that we are using prime operating dollars to make this happen.

Agenda Item: Center's Representatives report on Future Regulatory Challenges from each Center and OC representative

DR MEYERS: What I am going to give you is not so much an overview of problems, but an overview of research as it is currently being done in the Center for Veterinary Medicine.

In terms of the organization, we have an Office of the Director and an Office of Management that don't do research. We have an office which is unique to veterinary medicine, and that is the Use of Minor Species. This is an office mandated by Congress

to help facilitate drug approvals for minor species. By that, we are talking about aquaculture, sheep and goats, rabbits and minor food animals, for which there is a critical need for therapy, but for which there is not going to be an economic market in terms of profit margin for the drug companies to develop a drug in the absence of government's help and government assistance. It has been useful to get several new drugs approved for aquaculture.

Then there is the Office of New Drug Evaluation and Compliance, and where I am at is the Office of Research.

This is a narrow view of the Office of Research at our Muirkirk Road campus. We are on about 165 acres of land with 73 staff. As veterinary medicine, we have large animal housing and the accompanying large animal surgery suites. When I say large animals, the smallest we deal with are dogs. Mice and rats are something we kill to get rid of because they are pests and vermin.

We do have a dedicated aquaculture facility which houses everything from shrimp to tilapia, and any type of fish, tuna fish or such that is used for food, we can and do have on site. We have a dedicated quarantine facility, because many times the buildings are full and if we need to bring in new animals we have to have a place to house them and make sure they are healthy to be introduced into the general population.

Since we have veterinary and agriculture animals, we do have to have pastures. We have about 15-two and a half acre

pastures. We have a dedicated feed mixing facility for the animals. In agriculture, one of the major ways you give drugs to animals is through feed. Since many of the drugs we deal with are either unapproved or illegal, there are unfortunately no commercial facilities that are going to blend those for us to use. We have the dedicated research labs to carry out the analysis of the different tissues and samples we collect from the animals.

We have three divisions within the office, resident chemistry, animal research and animal and food microbiology. Resident chemistry is just that; it is a group of analytical chemists whose main mission is to develop chemical analytical methods to detect drug residues in edible tissues, which are then usually migrated to the Office of Regulatory Affairs and state laboratories. Animal and Food Microbiology is just that; they are all microbiologists tasked with looking at issues of microbiological importance in veterinary medicine and agriculture. The main focus has been on antibiotic resistance for the last few years.

In Animal Research, we do everything else. All animal research is conducted within this division, all the pharmacology, toxicology, immunology and everything in between. We support the animal needs for the other two divisions.

Everything you heard this morning was focused on one species. CVM regulates everything else. From A to Z, if it is a

drug that is to be used in an animal species, we regulate it one way or the other.

We have four responsibilities. Pre-market, we are looking at safety and efficacy of both new animal drugs and new animal feeds. Post-approval, we deal with the adverse events of those same drugs and feeds. Post-approval, we pick up looking at marketed veterinary devices. We do not have pre-market authority over veterinary devices, so if you want to make money, come up with a test kit or a device for animals. Unless it causes a problem, you can sell it for years and we won't do anything about it. We also do compliance and research to support all the other offices.

We have oriented our research based around those four themes, so in terms of animal pre-market review, we have studies that are dealing with animals as well as those which do not involve animals. So we deal with things such as looking at animal drug safety as well as efficacy, mainly in the areas of model development. We deal with a lot of pharmacokinetic and pharmacodynamic studies, because a lot of the drugs that are being used in veterinary medicine are there because they have been grandfathered in for the last 20 to 25 years.

We also work with a lot of immunopharmacology, mainly in the area of inflammation-oriented research, as well as in the general metabolism depletion studies. Non-animal oriented studies

include things like chemical and drug development methods, looking for chemicals such as mycotoxins and other plant contaminants and drugs that might be in edible tissues, microbiological methods and antibiotic resistance.

In terms of post approval monitoring, the same things, looking at microbiological and chemical method developments to support the Office of Regulatory Affairs as well as state laboratories, coming up with new and better methods to detect the chemicals that are in edible tissues, and doing a lot of surveys, predominantly microbiological, but we are beginning to look at things such as distiller's brain.

Distiller's brain is a byproduct of the ethanol industry. Even after they have extracted the ethanol from the grain, it still has economic value because it still has energy content that can be fed to animals. The downside is that to maximize production of ethanol by yeast, they were throwing in all kinds of antibiotics to control the bacterial growth. Those are unapproved uses of the antibiotics that will go into animal feed.

Then developing new methods and validating the methods, so when we say they will affect just that method at that level, that work can be replicated in anybody else's hands.

In terms of compliance issues, pharmacokinetic and residue depletion studies are a major compliance action, because many of the drugs out there are grandfathered in because they were

on the market when CVM came into existence, so we have had to show that they are safe and effective.

Method validation trials: One of the key things we do at our Division of Animal Research is generate what is called incurred residue tissues. It is not sufficient to take a drug and put it into meat and extract it out and say you can get the method. When you give the drug to the animal it is handled differently in the animal, so you have to have actual tissue that has come from an animal that has been given the drug. That is kind of tricky, because you have to hit a certain target level in the tissue. A lot of times it is by guess and by golly, based on your best guess estimates. But the generation of those incurred residue tissues are an important part for not only our work, but we also support a lot of the ORA laboratories when they are developing their own methods, as well as other federal agencies such as Food Safety Inspection Service and the Fish and Wildlife Service, for instance.

Another thing we do is we also evaluate a lot of the screening tests. Screening tests are diagnostics, and they are on the market without federal oversight and without preapproval. So a lot of work we have been doing over the last 15 years has been to evaluate these tests to see if they actually meet not only their label claims, but meet our expectations. The work that has

been done with the evaluation of screening tests resulted in many of them being pulled off the market because they are ineffective.

Animal feed safety is probably one of the other key functions of CVM. An animal may not be sick, but it always has to eat. The food they consume has to be just as safe and wholesome and nutritious as it is for people. The three areas we are focusing on are long term prevention of BSC, bovine spongiform encephalopathy or mad cow disease. The only way that disease is spread is through feeding cattle the rendered remains of other animals that have the disease. You stop that by preventing the practice of allowing ruminants to feed on other ruminants.

That is one of the principal firewalls worldwide to the prevention and spread of BSC. We have been very active. Right now, the methods being used by the states and by ORA laboratories are methods we developed, validated and have migrated to them.

Chemical methods in feed are an important issue. There are different chemicals in there that are not supposed to be there, such as toxins, mycotoxins, other plant toxins, so we have to be able to detect those to make sure the grains that are going into the feed are safe for the animals.

Lastly, we are looking at a new area, which is looking for microbiologists' surveys in feed. You don't think about it, but depending on how you store the feed, the feed can develop and acquire different microbes which not only get into the animals,

but then can end up on the carcass, in the meat, and in the people through inefficient processing at the rendering plant or at the slaughter facilities.

So with that, are there any questions?

DR. HINES: So interactions with NCTR at all?

DR. MEYERS: We have had a lot over the years. As Carl can attest, we have had a long interaction with NCTR. They were the first lab to help us with the validation of the methods for BSC detection. There are other interactions with our preapproval staff and for issues on the microbial safety. That has been a big issue with us.

DR. HINES: Do you see any questions coming down in the future that NCTR could probably be even more helpful with?

DR. MEYERS: One of the things we are trying to get a handle on is what does nanotechnology mean to veterinary medicine? Veterinary medicine is the poor stepchild to human medicine. A lot of the products we get are failed human drugs. Anteroflaxin is one of them that failed in humans and came to us.

We are also behind the edge in terms of the products we get, because the profit margins aren't there. There aren't insurance companies to insure your herd of cattle against disease. So that is one area where we see it coming, but we don't know what it means to veterinary medicine yet.

DR. MOORE: I might also mention that we have had some interactions with the gene toxicology people for one, but also with people that are doing some of the risk assessment and quantitative cancer risk assessment. We have been talking with them.

Just last week, one of the risk assessment people from CVM and I participated on a case study that was done for risk assessment meetings. So I think there are quite a few collaborations with CVM.

DR. MEYERS: One of the other things I was thinking of during the meeting is something that is near and dear to Peggy's heart, which is the whole issue of human food safety. Anytime a drug is going into a food animal, there has to be an assessment as to whether the residues are going to be allowed pose a threat to human health. That is always a difficult assessment to make, if only there were a better tool to help make that assessment.

PARTICIPANT: Going in the other direction, has there been any effort, or would it be of any assistance or help to NCTR to rely on the expertise at CVM for extrapolation of animal data to the human, given your expertise in the animal systems?

DR. MEYERS: It would depend upon which animal system you are talking about. For humans, it would be difficult for us, but we obviously do have the capability to do just about any food animal there. I listened to the discussion this morning about the

100-pound mini-pigs being big which was ironic, since I just finished a study with 130-kilo pigs. So yes, it can work both ways.

DR. MILLER: When I was in Women's Health we funded Jurgen von Bradow when he was still with the center. He had dairy cows. We were just asking the question, do drugs that are used for lactation partition into milk, just as a model. They could get tons of blood and they could get tons of milk, and just ask that very simple question, do they sequester into milk?

When I was at CVM that was always a question. If you treat a dairy animal with a drug, how much partitions into milk? They have quite a good collection of data to use just to ask those types of questions as well.

DR. HOWARD: To answer your question about the extrapolatability of animal work to humans from veterinary animals, that is something that is not unique to us. It is a problem all throughout regulatory agencies. Like the collaboration with NTP, looking at cell-based dosimetry as opposed to gavage-based dosimetry is a direction in which we have been moving for awhile, and they certainly help with extrapolatability.

DR. AFSHARI: Thanks, Mike. One thing I wanted to ask about is about the work we are doing with some of your colleagues on melamine and cyanuric acid, a very important study. Even though the dog food incident is now about two years behind us, we

know that a year ago there was an outbreak of poison that is thought to be related to melamine in infants in China. So this issue hasn't completely gone away, even though we can test for it and that sort of thing.

I know those studies are ongoing, and those are very important to both us and you in terms of looking at ways to treat and also combinations of melamine and cyanuric acid that are especially harmful.

The other area that I wanted to ask about is your animal populations. I imagine you run across some of the same issues we do in that you have maintenance costs for those animals. So do you bring in fresh animals for each study? Or do you actually breed and maintain some of your animals on-site?

DR. MEYERS: The only animals we maintain on sites are a small dairy herd. Other than that, we bring the animals in on an as-needed basis. We have identified several suppliers for swine in terms of getting into quality or research grade animals. In terms of cattle, we have identified sources where we can get good animals, but they are not obviously research grade.

The reason why we have dairy cattle on-site is because, historically, we found when we needed to develop a method for looking at drugs in milk, the only way we can be sure that the animal is 100 percent clean and free of all drugs, is if we have

total control over the animal start to finish, and know exactly what it did and did not get.

PARTICIPANT: In doing this, it would seem like it would be beneficial to be able to screen them quickly. So I imagine you have microbiological support and veterinary colleagues on staff to handle all these needs for quality control of the animals.

DR. MEYERS: Yes, we do. From the study we just finished, we had excellent support from our microbiologists to look at the microbial health of the animals. We have two world class veterinary surgeons on site. One of them is our current division director and the other is our new attending veterinarian. Both are highly qualified in large animal surgery. In fact, our division director is board eligible in large animal surgery.

DR. WILSON: The mission of the Center for Biologics is to ensure the safety, purity, potency and effectiveness of biological products. The products we regulate are very diverse. I am going to go into that in a moment.

The vision is to protect and improve health, both individually for the public in the U.S., and where feasible, we are also trying to partner with our counterparts globally to address public health concerns.

We facilitate development, approval and access to safe and effective products, promising new technologies, and we want to strengthen our Center as a preeminent regulatory organization for

biologics. Importantly, a major driving force for this is to use innovative technology to advance the public health.

As I mentioned, the kind of products we regulate are varied. They are very diverse. These are complex products. It includes everything from all the blood transfusions people get, components of blood such as platelets, derivatives of blood such as recombinant proteins that would have normally come from blood such as Factor VIII, vaccines, preventive and therapeutic, allergenic products, which are just gamisch things, related devices, for example, to isolate cells, all the human tissues that are used for transplantation, and then cutting-edge medicines like cell and gene therapies, and xenotransplantation products.

Now we have a new challenge that is coming because of the new legislation that requires us to develop a regulatory framework for approvals of what are called biosimilars, or generic biologics. That is going to be a new challenge facing our Center.

Our organization is in the center flask, the Center Director, Deputy and Associate, and then we have seven offices that support the Center. For those of you who are overly analytical, there is no meaning to the use of a petri dish, but I did use Eppendorf tubes to signify these are the four offices where we have some research component. It includes both non-laboratory based research such as Biostatistics and Epidemiology and then the three laboratory based offices, Cell Tissues and Gene

Therapies, Vaccine Research and Review, Blood Research and Review. Then the three offices above help support the whole Center management, communication outreach and development. And then the Office of Compliance of Biologics Quality is where we also have a laboratory based Division of Product Quality that does low release testing of certain approved biologics.

We have a very active research program in the Center for Biologics. Much as you have heard today from Bill Slikker and others, we see our research component as having a critical component to addressing public health and fulfilling our regulatory mission. So we see it as cyclical. As a public health issue arises, that drives the development of a novel biologic product. Sometimes this presents regulatory challenges in terms of how we regulate it. That is where our research can both provide a mechanism of discovery, development of new tools, standards, reference materials and so on. By having this new information, these new methods and so on, it helps to develop and inform development of regulatory policy, decision making and then hopefully we get improved data as these products develop from the sponsors. That allows us to make a more educated decision as it becomes a license application in terms of evaluating benefit versus risk. Then hopefully developing and finally resulting in a licensed product that is safe and effective, and having a positive impact on that public health issue.

Our Center is somewhat different. We have what is called the researcher regulator model. This means that all of our research scientists also spend up to half of their time doing regulatory work. They do the same activities that our fulltime review scientists do. That means they are reviewing submissions, they are going out on inspections, they are writing guidance documents, they present at advisory committees, they organize workshops and so on.

This means that our research scientists are right there looking at the information and understanding what the scientific gaps and challenges are in regulating these products. So this allows us to be able to use our research expertise to address these problems in a very timely way and hopefully make it useful to our regulatory decision making process.

I wanted to finish by mentioning these workshops. As Bill mentioned, we had two workshops this past year. They were very successful. We had one with the Division of Microbiology and another with Jim Kaput's group. The first was with the Division of Microbiology on June 9. The way we develop the workshops is, we provide NCTR some information about the scientists we have. They provide information to us, and we hand pick the scientists we think would make the best pairing, in the sense that they have similar interests, but not completely overlapping.

The outcome of the micro research is that we strengthened one ongoing, scientific collaboration in the area of corona viruses. We have developed new collaborations in the area of the anthrax GI model Carl mentioned this morning. We have been exchanging information. We had an endothelial cell model for looking at anthrax toxicity.

Another area of interest to us is anthrax with the neuroscience expertise that is here at NCTR, so we are starting to engage in that area. Then importantly we have now strengthened collaboration among CBER, CDRH and NCTR scientists to look at biomarkers of hepatitis C virus-related liver toxicity.

The second one which was the next day only by coincidence, not by design really, was in stem cell biology. Again, we had a fairly focused workshop of scientists with mutual interests. It really was a great opportunity for us to make sure we didn't have duplication of efforts in this very important area between our two Centers.

What was nice is that it improved communication between the two centers. For example, Jim Kaput has developed an e-room, giving scientists with interest access to this. We are talking about collaborating on development of this Wiki database to collect the meta-data related to stem cell experiments. We are gaining from the expertise here at NCTR to look at epigenetic status. As Jim mentioned this morning, they have the capability

to look at methylation. We had expertise in flow cytometry that has helped them improve their ability to use flow cytometry on these stem cells. We have also identified potential areas for future collaborations.

I wanted to just finish with the benefits of the workshops, which is, improve knowledge of the ongoing scientific programs across the Centers, identify ways we can provide scientific synergy between the two Centers, avoid redundancy in the programs, but help enhance the science and expertise that is being focused on these important areas.

So as one example in the stem cells, we realized there is a very different focus of the work in the two areas, but there is a lot of complementation of the approaches, and there is a lot of opportunity for synergy in that area.

I will stop there. The last two slides are just for your reference. Any questions?

DR. BAKER: I know a lot of pharmaceutical companies are starting to ramp up biologics research and vaccine research. A couple of questions: Do you see a gap in the near future in terms of your capacity to handle all the biologics that are going to be coming through the pipeline? And where are the technical gaps you would like to fill as well?

DR. WILSON: I think we certainly can always use more resources. As you may know, there is a medical countermeasure

initiative that has been discussed that may bring some additional resources to our Center to focus on that particular area, which is of course heavily vaccine oriented. That will help us enhance not just our regulatory expertise, but also our research programs as well to address the scientific gaps in those areas. That is not definitive, but it is something that is being discussed.

In terms of scientific gaps, I think for us, the big challenge that we are looking at right now is in the area of biosimilars. With these very complex products, it is not like a drug you can throw onto a HPLC and say here is the chemical structure we got at the end. These are living organisms. They may be live viruses for vaccines or whole living cells for cell therapies and so on. So how you address that is a big issue.

We are very concerned about, as was discussed this morning, with the issue of immunogenicity of recombinant proteins. That leads into personalized medicine and why some people develop an adverse response in the form of an immune reaction and others don't. So those are some of the big issues. I could go on for days, but I won't. Thank you.

DR. HANIG: First off, let me apologize for the informality of some of my slides. I think it is almost impossible to characterize all of the different activities of the Center of Drugs. It is a very large Center, maybe one of the largest.

There are an awful lot of things that are happening in a lot of different areas.

I put this slide up just to give you an idea of the number of offices we have. These are mostly super offices. What that essentially means is that there are smaller offices within them.

I guess a good example might be the Office of Translational Science that has the Office of Clinical Pharmacology and the Office of Statistics. As you all probably realize, the biggest part of our mission is to evaluate the safety and efficacy of new drugs and to ensure that the existing supply of approved drugs are safe and efficacious.

There are a considerable number of compliance issues. The Office of Surveillance and Epidemiology is very much involved in looking at various post-marketing signals. These signals are often not very strong, although the use of pathway databases and techniques has really strengthened these.

You can see that we are dealing with a lot of different activities. The Office of Pharmaceutical Sciences is highlighted or de-highlighted there, because that is the only office that has laboratory facilities.

So if we go to that, you will see that the Office of Testing and Research has four divisions, the Division of Applied Pharmacology Research and the Laboratory of Clinical Pharmacology.

These are in the process of being combined, and it will be the Division of Drug Safety Research, but I didn't put it up because it hasn't been signed off yet. So those two divisions are mostly concerned with pre-clinical work on the one hand and clinical pharmacology aspects on the other hand.

The Division of Pharmaceutical Analysis is in St. Louis. It is our analytical arm. The Division of Product Quality Research is at White Oak, and deals mostly with laboratory issues of generic equivalency and with issues of formulation and extended release. They are so complicated that they really require full-time attention.

There is also the Office of Biotechnology Products, the Division of Therapeutic Proteins, and the Division of Monoclonal Antibodies. They are dealing with a lot of things similar to those mentioned in the Center for Biologics, biosimilars, large proteins and so on.

The Office of Generic Drugs and the Office of New Drug Quality Assessment do not have laboratories. I guess the Office of Generics is the largest. Congress has just appropriated more money for maybe hiring up to 50 people. The Office of New Drug Quality Assessment is the chemistry assessment arm of the Office of New Drugs. In other words, they do all of the chemical evaluations before a drug is approved.

So having said that as an introduction to our organization, I would like to focus mostly on what our priorities are and what our needs are.

The Science Prioritization and Review Committee, or the so-called SPAR Committee, is a relatively new committee that was organized by the Research Coordinating Committee that is chaired by the Deputy Center Director. These are their priorities: to develop quantitative methods and tools for analysis of benefit-risk and enhance detection of adverse events; to improve risk assessment and management strategies to reinforce the safe use of drugs; and to evaluate the linkages between product quality attributes, manufacturing processes and product performance. An embodiment of that is quality by design, an idea where you establish a design space, and if you can control everything inside that space, you can guarantee you probably have a safely manufactured product.

These are goals and priorities: to evaluate the effectiveness and impact of all regulatory communications to the public and other stakeholders; to develop and improve predictive models for safety and efficacy in humans; to improve clinical trial design, analysis and contact, and to enhance the ability to individualize patient treatment.

The embodiment of these things is essentially some of the critical path goals and objectives that have been put out recently.

This is a CDER list of priorities for 2011. They are not necessarily in any sort of priority order: biotechnology and biologics, counterterrorism, quantitative methods, clinical design, applied drug safety, communication, research, bioinformatics and so on.

But within the framework of these priorities, these are some of the critical path topics or areas for which research has been encouraged. Better evaluation tools, streamlining clinical trials, harnessing bioinformatics, moving manufacturing into the 21st century, developing products to address urgent public health needs, and targeting things for specific at-risk populations, and pediatrics is a very good example.

With that in mind, I should add a very special critical path thing for generic drugs. Generic drug approval really started several decades ago. When you get right down to it, the complexity of formulations today makes it somewhat problematic; we will always hit the target in terms of using the one, two or three parameters we call for.

Some of the goals are to improve the science underlying the quality by design to develop and manufacture generic drug products, to improve the efficacy of current methods for

assessment of bioequivalence for systematically acting drugs, including products that use complex and novel drug delivery technologies, and to develop methods for the assessment of bioequivalence of locally acting drugs such as topical inhalation products.

I recently saw a very exciting presentation where an MRI was used with Helium 3 and so on to characterize the whole tracheal bronchial tree in a very dynamic fashion. Also used were fluorescent gases so you could actually see the dose delivered. Most of the concentration has been on delivery devices and particle size, but it really doesn't tell you what gets down there. That raises a lot of questions about generic equivalency, as does developing methods for characterizing complex drug substances and products.

So these are some of the critical path things. As I said earlier, we are very grateful to NCTR for appreciating our needs. I thought I would put up some examples of ongoing projects conducted at NCTR in response to CDER's needs.

You have all heard about the neurotoxicity of ketamine in pediatric animal models. It hasn't been resolved, but we have made some extraordinary progress on it. What are the long term consequences of neonatal ketamine anesthesia in rhesus monkeys in terms of cognitive assessments? We are coming to a point now where we can make some statements about that. They are very

dramatic. I won't go into it because Merle will tell you all about that.

A relatively new critical path project involves improving prediction and monitoring of drug safety through assessment and simulation of injury reserve and repair pathways.

Development of MR imaging and informatics techniques for tissue sampling to guide and confirm classical neuropathology: With this project we hope we will be able to use MRI to inform and create three smart slides instead of just three ordinary ones.

Studies comparing the neurotoxicity of amphetamine, methamphetamine and methyl phenadate: These compounds, when abused, really destroy the blood-brain barrier so that has a lot of implications for safety.

Finally, we have gotten tremendous metabonomics support for a whole variety of preclinical safety model development projects for NCTR, and it has really helped us out tremendously. I hope you are able to continue that.

So, that is the end of my slides. I would like to finish up by simply mentioning some of the areas I think will represent future needs. We will always need to develop new safety models. That is a given. We will always have to respond to emergencies and ongoing problems with approved drugs, whether we have to take them off the market or we have to modify it, put a black box around the label and so on. This is something that will

continue. We will always count hopefully on NCTR to help us out with this.

But some of the more esoteric things I see are, number one, getting involved in post-marketing toxicology research problems, the issue of idiosyncratic reactions and so on. When a drug is approved, it probably hasn't gone into more than a couple of thousand individuals, and maybe as many animals. All of a sudden, millions if not hundreds of millions of doses are going into middle aged people, possibly for the rest of their lives. We have been extraordinarily lucky that our system works.

I am of the opinion, it is just my opinion, that drug companies ought to continue their research in the interests of saving their drugs. It only takes five liver transplants and five deaths to get a great drug off the market. That could be hundreds of millions of dollars and many, many years of use for the public that is going to stop.

So it is really a race between the drug and the researchers as to who is going to get to those vulnerable populations first and cut them out of the exposure. That is a really important thing. Anybody can come up with a scheme for doing this, with all of our new tools, databases, all kinds of informatics, pathway analysis and so on, because the epidemiological signal isn't that strong.

I think the aging population and those with predisposing conditions in the context of all these older people getting drugs for so long really merits animal models and aggressive research in that area. I hope people think it is important enough to address.

The safety and efficacy of nanotechnology machines: We have all been talking about nanoparticles, but we have reached a point now where we are seeing drugs encapsulated inside of many layered dendrimers with antibodies for targeting on the outside. These are machines. I don't know whether they will be classified as devices or not, but the effort that has to go into guaranteeing their safety and efficacy, I think, is a real challenge.

Carolyn went into the whole issue of biosimilars and follow-on products. That is also a problem for one of our offices I showed you earlier. I am hoping people step up to the challenge, because I don't think it is going to be as easy to establish equivalency. It is really an awesome thing to approve something because it looks similar. I won't get into a lot of the issues there.

I think everything that is done on behalf of CDER is going to be helped tremendously by all of the efforts done at NCTR on biomarkers, and particularly, imaging. We are hoping to get all kinds of assistance in the future with our projects using these techniques, and that process has already started.

Then finally, I will just mention the issue of immunogenicity of large proteins. It is not the kind of experiment you can do in rodents, but I did hear some very exciting news about various experiments that have succeeded in humanizing mice. You start out with an immuno-compromised mouse and grow in the human reticular endothelium system, and pretty soon you have a mouse with a human immune system and so on. So that offers some very exciting possibilities in the future.

We are also starting to take a look at the potential for cancer in immuno-compromised patients who are receiving various drugs. These are some of the challenges. I think in the interest of time I will stop here and take any questions you might have.

DR. AFSHARI: I will open it up for questions for Joe from the SAB.

DR. BAKER: You mentioned working on predictive models and safety and efficacy. Is that a translational medicine point of view or personalized medicine point of view? What do you mean by predictive models?

DR. HANIG: I think the greatest goal is to be able to translate whatever we find in animals into use in humans. But very often it is an iterative thing where you go back and forth.

My understanding is that treponins, which are being utilized now to predict cardiac injury, got their start in humans more than in animals. Then they went back to animals and modeled

it there, where they could perform a lot of experimental procedures, do pathology and so on. What we have learned from that makes the translation into humans better. So I think it is back and forth. Does that answer your question?

DR. WATKINS: The issue of postmarketing adverse events: you suggested that we should encourage the drug companies to continue to do the research after the fact as a means of protecting their market. But if they find adverse events, they are at a likelihood of having the drug pulled or at least having a black box put around it.

How do you anticipate incentivizing the drug companies to be on the lookout for these adverse events, which I agree with you, would be to their advantage to identify a subgroup you could factor out of the equation, and therefore save the drug? But at this point it is not to their advantage to do so, because you don't have the mechanism for being able to take that last step of factoring that subpopulation out. So it leads it back to the FDA to do the post.

DR. HANIG: I have always felt that getting an approval for a drug is not a gold-plated license to become rich and ignore any moral obligations. But that is a very idealistic answer.

If there is an adverse effect short of deaths and so on, we want to hear about it from the drug company before we tell them about it. So that aspect of the paradigm is out there.

I really think their chances of making discoveries that would protect vulnerable populations within the framework of our current knowledge and approach is a lot better than suddenly having a big ordeal, rather than keeping their head in the sand and making money.

I look on it as a much more advanced and progressive way to look at things. I am hoping they would see it that way too. But I don't advocate this as a policy for the agency. It is my personal opinion, and I said that earlier.

DR. WATKINS: More of a comment. The challenge in these very rare adverse events is not just that animals aren't good models, but humans aren't good models; it is that one in 20,000.

DR. HANIG: You are absolutely right.

DR. WATKINS: So I think it is very hard for the drug company, once they identify someone who has had a horrible, serious reaction, to get their cooperation to participate in additional studies. There are networks, and I know CDER is making very good efforts to be involved with them, like the Severe Adverse Event Consortium and the national Drug Induced Liver Injury Network, where these are not signal detection, but research efforts to find these people, to study their genes, and in the case of the Drug Induced Liver Injury Network, to study them and keep the identity links. We know it is not all genetic.

I think that is certainly one of the most promising areas to be able to figure out what is special about these people and how to identify them, and ultimately to get the mechanisms to design safer drugs from the beginning.

I know CDER is doing everything they can. There are certain political boundaries between the NIH and the FDA that has prevented full cooperation, at least in the Dillon Network effort, and I think also in the Severe Adverse Event Consortium, since that is an industry consortium.

Anyway, maybe we can help solve some of these things by putting some of these comments in the recommendations.

DR. HANIG: I think you raised a very important issue. There are ethical and patient protection issues. When I said research, I was really indicating efforts that utilize the newest techniques for enhancing epidemiological signals, the use of pathway analysis and other things that haven't been available in the past.

It would be a research effort initially, but I think it shows a great deal of promise. We certainly can't advocate it using past or contemporary methods right now. The old concept was the mega mouse experiment. It was done here, and we know about that.

I think we need new concepts to go forward in this. I am reminded of the story of how, at the turn of the century, they

didn't get the exact atomic number or molecular weight, and it bothered them, so they kept building brand new, better and better analytical balances. They didn't know about isotopes.

DR. WATKINS: Can I just make one more comment? It is taking the opportunity to be in the bully pulpit. But it is these rare adverse events that are becoming the bottleneck to delivering important drugs to people.

An example would be rivaroxaban, the oral anticoagulant that an FDA Advisory Committee recommended approval for a year and a half ago, and the drug is still not approved because the FDA is waiting for larger and larger databases. The issue is not whether it works. There is no question it works, but the issue is, is it safe in every single person who takes it?

We know of another case of a diabetes drug where there were two individuals with a little over something out of 4,000 and it was not first in class, but the company was told to do a one-year, 20,000 patient study. Just looking for rare events, if you do the math, you probably wouldn't even see in 20,000 patients treated for one year. This is a huge issue, and everybody knows it, but because it is like epigenetics five years ago, there is no easy way to study it, and people tend to ignore it.

DR. HANIG: It is a huge problem.

PARTICIPANT: Thank you, Dr. Hanig.

DR. GRAY: I am going to use some of my time to share with you my own personal experience, a little bit of it, anyway. I was in medical research for 20 years, doing the traditional, academic NIH grant things. Then I went to FDA two and a half years ago. FDA is a very big place; lots of stuff going on. I am in the research arm of the Center for Devices and Radiological Health.

I would like to share what Bill is talking about in making people more aware. I don't know if he has made efforts to be in our laboratory and go from lab to lab or from division to division, but I will show you the different divisions here. If so, it hasn't trickled down to someone like me who is in the lab most of the time.

We get a lot of e-mails. I got an e-mail that Donna Mendrick was going to be up giving a talk. It had a number of topics I was interested in; systems biology, patient specific medicine, so I said wow, this sounds great. I can't believe all of those people down here are doing all this great science and I didn't know about this. I will take some of the blame for that, but we are all busy doing our own things.

Then Donna was kind enough to invite me down, so I spent yesterday going through the facilities here. My specialty is electrical activity of the heart. I am a cardiac electrophysiologist. One of the things I think is important to

share is that, many of you probably know this, but with drugs there are cardiac arrhythmia side effects, which are detectable by the surface electrocardiogram, the ECG. I might call it a Q-T interval, but the ECG is nicer.

I gave a talk yesterday, and I met with a number of people from patient specific medicine to bioinformatics to multispectral imaging and gene expression in cardiac toxicity. My own specialty fit in with a lot of these different things, mostly for the reason I told you about. But it was just amazing for me to see the depth and breadth of what is going on here.

I don't have an easy solution for how to make those connections. But in my particular case, it is an example where my own specialty fits in with a lot of stuff that is going on here. I was incredibly impressed with the quality of the science, the motivation, and the breadth and depth of the science.

So with all that personal stuff, I will move into what I came down here to present. I would have done a little more research in putting this slide in for animal facilities if I had better knowledge of what I was supposed to present.

We have a lot of different devices we regulate at CDRH. I am involved in the pacemakers and defibrillators, but we have a lot of different devices, and we have an Office of Science and Engineering Laboratories. That is what I came prepared to talk about, and probably is the most relevant to this group.

Who is the Office of Science and Engineering Laboratories? That is one of many offices at CDRH. We have about 180 staff, mostly scientists. We are very top heavy. That is one of the things we could use, and I think that is something that is being done very well here. We are moving towards more postdoctoral fellows and training. That is something we can use as well. We are trying to partner with universities nearby to have graduate students come in. That is something we could use a lot more of.

We have all types of scientists and engineers there. We have some clinicians in the research arm. We have medical officers in the Office of Device Evaluation, and I interact with them quite a bit in terms of the clinical type research I am getting more involved in.

What do we do? We do lab-based science to understand issues of safety and effectiveness with devices. We have in-house labs for regulatory science, not exactly like what you heard about before on regulatory science. In terms of devices, we do things like electromagnetic interference and radiofrequency ID interference. So there is a lot of work on the devices themselves. We do preclinical test method development, once again for devices, development of standards, lab evaluations, and forensic cases. Sometimes a device will come back to us and we

will do some work on that. We do technical reviews of regulatory files and we do training for CDRH staff.

That has been very successful. Recently, we have been presenting OSEL, Office of Science and Engineering Laboratory seminars. Who OSEL is has been the theme of the seminars, and they have been very well attended. They finish with a lab tour. They come down. For someone who has been in academics for a long time and does primarily research at FDA, it is nice to go to FDA, see that people are very conscious of what they are doing and motivated to do it, but also that they look to scientists who have information about mechanism of action, and that helps the regulatory decision process.

In terms of the adverse events, I couldn't agree more about getting information from the patient events. What we want to find out is the root cause. That is very difficult, but bringing in the scientists helps a lot in that respect as well, especially in terms of things like what I study, electrophysiology, where we have a good idea of a lot of the basic mechanisms.

Here are the divisions with OSEL. We have the Division of Biology, Division of Chemistry and Materials Science, Division of Electrical and Software Engineering, Division of Imaging and Applied Mathematics, Division of Physics and Division of Solid and Fluid Mechanics, a total of 21 labs if this is up to date.

One of the questions earlier was how much interaction has OSEL had with NCTR. I can't answer that. I came down here and learned that there was some collaboration going on with other people. Part of that is because I have only been at FDA for two and a half years, which in government life is a pretty short time. So I haven't been able to interact with these people as much as I'd like. I know there are people over at CBER I have been meaning to talk to for a long time, but that is part of reality. It is not just one Center to another, different locations across the country, but within one location.

This is something that Bill Herman, who is a really bright guy, works on. He works on ten-year technology forecasts for our office. This is something he does every few years. He puts a lot of effort into saying, from the office standpoint for devices, what we think is coming down the pipeline that is going to be very important.

Here is the list he put together. You are welcome to contact him with any questions or comments. Computer-related devices and systems, as we get more into the digital age and more records become available, that is going to be very important. Wireless systems, I don't have to say anything more about that. Minimally invasive technologies, implants, genomics, age-related technologies and portable home self care are also part of the list.

If you have any questions for me, I will do the best to answer them. I'm not as informed of the whole office and Center as most of my other colleagues, but I will do the best I can.

PARTICIPANT: Thank you. I appreciate the overview. It was good to hear about some of your research activities yesterday, really intriguing. I have already heard from some of my colleagues that they really enjoy interacting with you on some of these special issues of how to evaluate the cardiovascular tissue, in particular.

I saw the one up there about the age-related technologies and also about genomics, then the one about the minimally invasive technologies. I assume that may include imaging. I think that is an area I know you have technical expertise in; your Center does, as well as the idea that you are involved in the standards for imaging. We have been interacting with some of your colleagues on that note.

But can you give me a little more information about the direction you see imaging moving within the FDA in the near future?

DR. GRAY: I can only give you my own personal view. This came from Bill and is just a set of slides. I know them fairly well, but I don't know exactly what he meant by that.

I will take a pretty educated guess, though. It is exactly what you were saying, non-invasive imaging. What you saw

me present yesterday is, we inject voltage sensitive dyes into the heart to record electrical activity and give a very good visualization of what is going on in the heart. We would love to do that in humans, but these dyes are toxic.

However, that is not the end of the story. There is a lot of imaging, and there are a lot of probes. You put in things to enhance things. The multispectral imaging that is going on here is just phenomenal. As the technology gets more and more advanced, the research we can do is going to be more and more applicable if we can translate it.

I was talking to Jim yesterday. We were talking about finding a biomarker. It is probably going to be a combination of a few things to identify. So as we get more and more data, this place is in a perfect situation to combine the mathematics and the statistics with the data. The multispectral imaging; I was blown away by how you put on different coils and you can record different things.

To get all this data you can get from the animals and trying to start to put together and think about patient specific medicine and other things, and do it with some physiology in your head, these guys are in a great place to do that kind of stuff.

So I think that is where that is coming from. The imaging is just taking off in terms of the information and the

speed at which you can acquire things. The information is going to keep coming at us.

DR. FLYNN: I am doing something that probably should have been done earlier in the day. I'm sure a lot of people have heard references to CFSAN. I remember I attended a conference one time that was attended by people outside the FDA, and one of the panelists raised his hand and said, what is a CFSAN? That is our Center for Food Safety and Applied Nutrition. The acronym is pronounced CFSAN, so for those of you who have been wondering what that means, that is what that is.

Basically our mission is very simple, and in conjunction with the Agency's field staff. We are responsible for promoting and protecting the public's health by ensuring that the nation's food supply is safe, sanitary, wholesome and honestly labeled, and also that cosmetic products are safe and properly labeled. That is one thing a lot of people on the outside don't realize, that it is actually the FDA's Center for Food Safety that regulates cosmetics.

Here is the basic structure of our Center. We have nine offices. I guess the office names are pretty self explanatory, but I will try to point out, specifically, the offices that engage in the scientific, laboratory-type of research work.

One of the critical ones is the Office of Cosmetics and Colors you see over there on the left side. One of their

responsibilities is the certification of colors. They have a fairly large laboratory operation based on the analysis of chemical colors. Another key laboratory office within CFSAN is the Office of Food Safety. That is primarily chemistry and physics. They do a lot of the actual analytical work, analyzing foods, for example, for pesticide residues. As part of their program, they also work on the development of new analytical methods, but they also contain a microbiological component. Again, their concern is for the identification of microbial contaminants in food.

Another component in the Office of Food Safety is the Office of Seafoods. You all, I'm sure, are aware of the Gulf oil spill. The Office of Seafoods had a key role in that. Most of CFSAN is headquartered in College Park, Maryland. It is where we are headquartered, about 15 miles from the White Oak agency headquarters. But the Office of Seafoods has a satellite laboratory in Dolphin Island, Alabama. They were a key player in the Gulf oil spill.

They are actually a very key player in the day-to-day operation of the safety of seafoods. For example, whenever there are red tide events in the Gulf of Mexico, it is the laboratory that is responsible for determining whether or not it is safe to consume the shellfish in the Gulf.

I may be jumping a little bit ahead; this is a key issue of CFSAN, the Gulf oil spill. It is something that we couldn't

have anticipated. As we heard this morning, NCTR has already played a key role in that outbreak, and finding ways to identify the hydrocarbon contaminants that were in the Gulf seafood products.

Something that is still ongoing that probably hasn't been fully resolved yet is the chemical dispersants that were used in the Gulf. This was a totally unknown issue that nobody could have anticipated, but certainly one we still have to resolve, and one our Center and NCTR are playing a big role in resolving.

The other big research component on the right there is my home base, which is the Office of Applied Research and Safety Assessment. That building is located in Laurel, Maryland, about ten miles from the headquarters in College Park.

We are strictly a laboratory research organization. We provide regulatory support. Here are some of the things we do, which are very consistent with what NCTR does. We maintain a very close liaison with our counterparts at NCTR, and have worked together over the years on a number of joint projects. Even on melamine, we have a project going on within our building. We are collaborating with the Center for Veterinary Medicine and staying in close contact with our colleagues here at NCTR. Everyone is sharing the data on this. So as I said, there has been a long history of a close collaboration certainly between -- our acronym

is pronounced OARSA, by the way -- between OARSA and our compatriots here at NCTR.

Finally, just to give an overview. We have three divisions with roughly 25 to 30 scientists in each division. The first two, Division of Molecular Biology and Division of Virulence Assessment, deal with the microbial safety of foods. The division from which I come, Division of Toxicology, deals with the chemical safety of foods.

I think that is the end of the slides, if anyone has any questions.

PARTICIPANT: (Comments off mike.)

DR. FLYNN: Actually that brings up another issue too that I'm sure will be very closely involved with NCTR. There are a number of products already, cosmetic products, on the market that contain nanomaterials. That is a totally unknown, whether or not these materials are absorbed through the skin, and if they are and they metabolize in the skin, do they become systemic? So this is another area where I can see our Center -- since now they have the Center here devoted to nanomaterials. So I see another key collaboration with our colleagues at NCTR.

DR. BURCHELL: What about genetically modified foods? You didn't mention that. Are you working in that area?

DR. FLYNN: We certainly have the regulatory components. I'm not aware of any in-house research efforts devoted to

genetically modified organisms. We certainly do regulate them, and within our regulatory structure, we have the people to judge the tissues that come up and market these products.

DR. MEYERS: Can I just add, genetically engineered salmon is front and center at the very high levels of FDA right now, in trying to determine what the right approach is to regulating that. I think we have held a few public meetings to try and get some input on that. There has been a lot of press coverage, mostly con, some pro, on the public meetings.

So the Commissioner's office is thoroughly engaged in that discussion. Dr. Sharfstein, our principal Deputy Commissioner, is taking a personal interest in shepherding that issue.

PARTICIPANT: What do you see as the upcoming issues?

DR. FLYNN: I guess if the Gulf Coast incident is any indication, it is the issues you can't anticipate. I think it is just maintaining the strong scientific base we have here at NCTR and the components we have associated with CFSAN, as well, to be able to respond quickly.

It amazes me how quickly within our shop we geared up once the oil started pouring into the Gulf. Very quickly, our people recognized this is a potential problem, and started doing things to look at it. I know the same thoughts occurred down here in Arkansas as well.

DR. HINES: One comment on the Gulf spill. It is coming from an academic center; what happened to us is, we were excluded from research, literally banned and had samples taken away from us, et cetera. Was there any kind of activity like that with the efforts? Otherwise, were you prevented from doing certain kinds of research with the Gulf oil spill?

DR. FLYNN: Not that I am aware of.

DR. AFSHARI: I would like to invite Dr. Ferrar up from the Office of Foods.

DR. FARRAR: I just want to fill you in a little bit on one of the newer components of FDA some of you may not even be familiar with. It is called the Office of Foods, and it is where I work.

The Office of Foods was established by Commissioner Hamburg about a year ago. The reason for establishing the Office of Foods that Commissioner Hamburg communicated was to functionally unify and elevate all the various food programs scattered throughout FDA, those in CFSAN, CVM and ORA.

In the creation of this Office of Foods, a brand new position was created, the Deputy Commissioner for Foods. Mike Taylor, a longtime food safety individual with decades of knowledge and experience, was selected by the Commissioner to be the new Deputy Commissioner of Foods about a year ago.

Mike hired me about nine months ago. The Office of Foods is engaged in trying to do what we were charged to do, unify and elevate the various foods programs. A couple of things Deputy Commissioner Taylor got off the ground to help this effort were, number one, he established an executive leadership team, which includes the Center directors and the Deputy Directors for CVM, CFSAN and ORA, along with other Office of Commissioner's representatives, to come together as a leadership team for the foods program, help us gel, help us understand what is happening in each of the foods programs, and begin to come up with a plan for moving forward collectively.

Another effort Mike saw as critical right away was establishing a group of individuals to look at our core programs and core issues in the foods program. He did this by volunteering about 100-plus people from the field and headquarters to come together under ten core groups, ten activities within the foods program, including things like resources and planning, emergency response, prevention, inspection and compliance, science and research and so forth, to take a critical look from the beginning at these core areas of foods and look at how we are doing business, how we should be doing business, and how we can improve that.

Those ten core groups have met over the last year, actually about the last eight or nine months. We are finalizing a

report from the meeting that will be provided soon of what we are going to do in the near future as a result of this. Some of them have proposed ongoing projects, as you can imagine. Some of them have felt like they have done their work and those groups need to be concluded. Some of them are morphing into other longer term components.

One of those morphing groups to have direct relevance to NCTR is the science and research core group. There is obviously a very strong need for some ongoing work in that area to ensure prioritization, strategic planning, and continuity. So Commissioner Taylor has developed a plan with the executive leadership team to construct an ongoing steering committee, a science and research steering committee. It will be composed of volunteers from the Centers, from NCTR, ORA and other Commissioner Office groups.

The charge of that steering committee will be to develop a foods program science and research strategic plan in fairly short order. If some of you in the room have been drafted to be members of that group, Commissioner Taylor will make an announcement in the near future, and you will see some work coming out of that group hopefully very soon.

We think there is some low-hanging fruit in there that can show immediate benefit. You have heard a lot of presentations today, especially in the foods program, along the lines of methods

development and methods validation. There are numerous pockets of methods development and methods validation work going on throughout the Centers on the same organisms, on Salmonella, on E.coli 0157, and on Campylobacter. There is a need to bring that methods development and validation work together to gain some efficiencies there. So that will probably be one of the short term efforts in that group.

Not to stand between everyone and dinner or happy hour, but one of the areas that the Office of Foods has been very engaged in is the issue of the pending food safety legislation in Congress, that would give FDA much needed authorities in many areas, including imported food, new administrative authorities, and mandatory recall authorities. These are critical to how we do our jobs in headquarters and the field on a daily basis.

Unfortunately, we got this close this year, we think. We had broad support from industry, consumer groups, bipartisan support in the legislature, and it came down to one Senator voicing an objection because he didn't like the bill and hadn't voiced a previous objection. It is quite a system we have when one individual can stand in the way of significant improvement, remarkable improvement, in a food safety system.

But the bill is not dead. It may be on the ventilator and have a pacemaker, but it is not completely dead. After the

elections, there will be an opportunity for Congress to bring this back up again. We are keeping our fingers crossed.

With that, I see we are getting close to 4:30, the magic hour. I think I will stop there. I appreciate being invited out. This has been a tremendous experience and exposure for me to learn a little more about NCTR and all the great work that is being done. Thank you.

DR. BURCHELL: I haven't heard the word used today, nutraceuticals. There is a lot of concern that a lot of people are taking these on their own and not reporting them, and probably are responsible for some of the adverse events we see with drugs.

What is the need for quality control? It seems to be a big problem with what people list as ingredients and what is actually there. So how are you addressing that?

DR. FARRAR: I will turn to Tom for some input on that. I am going to claim a little bit of a rookie status here, having only been with FDA about ten months.

My preliminary answer while Tom is getting ready is, DSHEA put FDA behind the eight ball, in terms of us having to prove that these products are harmful rather than companies proving they are safe.

PARTICIPANT: It was actually John McCain that introduced a bill in February of this year, which he withdrew about 30 days later, over the objections of one of his Senate

colleagues that would have granted FDA considerably more authority in the regulation of dietary supplements. But as Dr. Farrar pointed out, the existing law pushes us back to pre-1906, where the total burden of proof that a dietary supplement is unsafe is on the FDA, as opposed to every other product we regulate, where the burden of proof is on the manufacturer to show that the product is safe before it can be marketed.

PARTICIPANT: That is kind of where we come in. We are looking at a lot of these remedies and dietary supplements. We are working closely with our people at the FDA to design our studies to give them the data they need to help address those issues.

DR. FARRAR: I will just put in a quick plug here. There was some mention from the Center for Tobacco about not competing for funds and how nice that was. That is a great position to be in. Unfortunately, the foods program, by and large with some exceptions in CVM, doesn't enjoy that luxury.

One of the things I have been remarkably impressed with, coming from the state of California public health department after 15 years, is how incredibly under-resourced our foods program is for the mandate that it has. It is just mind boggling, how few resources the food program has. We were hoping, through the food safety legislation, resources would help that situation, but we will see.

DR. AFSHARI: Thank you very much. We are actually not done. We have two more folks here on the right-hand side of the table.

DR. WHITE: I would like to thank you for inviting me today. I have actually learned quite a bit about NCTR.

I am going to use that last question to launch into some of the stuff we are working on, these nutraceuticals. We are working a lot with dietary supplements. We have a large initiative. We have two reports so far. Goldenseal was one of them. We have a couple coming through this next round of technical reports that was talked about earlier.

As toxicologists with the National Toxicology Program, over the last couple of years, we have started to work closely with the people at NCTR and other divisions of CFSAN to try to identify your needs at the FDA, since a lot of the work we do is used by regulatory agencies worldwide to determine the safety of these foods or dietary supplements or herbal remedies.

We have started at the design phase to bring people in to discuss some of the issues early on before we get these studies underway, so we can have some input as to what type of data you guys could use. I think with the dietary supplements, one of the issues has been, if something was on the market before 1994, it almost takes deaths in humans or human data. So we are trying to help out the best we can when it comes to addressing those issues,

but there is only so far the animal data can take us. I think that as far as the regulation is concerned, there needs to be a little more human data in combination with our animal data.

DR. AFSHARI: Thank you.

DR. HANIG: Just one quick comment on DSHEA and how it relates to that. It is true; we are cranked back to the point where the burden of proof is completely on FDA. But we still have the remedies of seizure and injunction and the issues of imminent hazard. An awful lot of these things are full of heavy metals. We do have the capability of characterizing these things. I think we have a much better chance of demonstrating the garbage that is in there and saying it is an imminent hazard rather than relying strictly on animal data to show safety issues because they are so complex. It has happened on a number of occasions.

DR. WHITE: I think one of the issues we have had in testing these things is, what do we test? We take something like Echinacea where you have different types of preparations. I have a couple of chemicals in my portfolio I look at, and there isn’t a standardization of these things in industry.

One of the things we have coming through in the near future is energy drinks. These are mixtures of a bunch of different types of compounds, and they are not consistent one energy drink to another. There are different components. Sometimes they are just listed as proprietary blend, so we don't

know exactly what is in them. We don't know if they are adulterated with anything. It doesn't seem like you guys have enough authority to go in and push them to define what is in there.

So that is one of the issues we are having. That is one of the reasons we are trying to work up front with the FDA. It is so we can get to the tail end so people don't say that is not what we use, and then the data is a waste and we have spent millions of dollars for nothing.

DR. HINES: One of the first things Linda did when she took office as new Director of NIEHS was to open the clinical research facility there. Can you comment at all about if and what type of clinical studies the NTP is engaged in?

DR. WHITE: I'm not aware if we are doing anything directly yet, at least anything that I have been working on. I know that energy drinks has been something I brought forward into the program. That is one of the opportunities we have with these energy drinks.

I would like to talk to Dr. Gray on some of the things he mentioned with cardiac issues, but that is something that has been talked about for things coming up. We have that opportunity now to take a look at some things in humans. We can have them take energy drinks. We can measure blood pressure, we can look at EKGs, and things like that.

As far as I am aware of, I don't know of anything that is planned right now. I know there was some stuff with bitter orange; I don't know if we have actually done anything yet.

PARTICIPANT: One thing that is being talked about is a real need to do careful studies with Bisphenol A in humans. That I have heard is going to be done in the Center.

PARTICIPANT: There are very few studies out of the 41 million or so. There were one or two human studies, and that was it.

DR. WHITE: I think there was some talk also about doing some exposure to bitter orange. I don't know if anything ever came out of that; there were some initial discussions, but nothing I have seen go through yet from NTP.

PARTICIPANT: I have one question. Certainly NCTR and NIH SNTP are intertwined with a significant amount of shared resources around testing compounds, nominating and testing compounds through the NTP bioassay piece.

As we look to the future, how we are testing compounds today doesn't scale very well against the enormity of the number of compounds out there with questions against them. So obviously there is research going towards new methods and new applications for testing that are going to allow us to potentially make a dent in that. But where do you see the immediate needs for collaboration towards that goal versus longer term pieces? And

how do we best guide the research programs here at NCTR towards those efforts?

DR. WHITE: That is a good question. We have a large effort in high throughput screening technologies to try to identify some chemicals that would be of higher interest.

A lot of questions earlier have been raised about priorities and how we prioritize things, and how NCTR prioritizes things. I know a lot of people have said that gets past us and it goes to the NTP.

Just a comment about the NTP and prioritizing things, we look at things when they come to us. We look at a number of different issues. We look at how many people are exposed, the level of exposure, the amount of a compound that is inputted or produced each year, and we try to get the most bang for our buck in the sense of what is going to have the highest public health impact. It is hard to look out at the end of the horizon and see, and as someone just said, what we don't expect, or what you can expect. But we have moved towards a lot more complicated things.

I am a newer staff member there. We joke around about how all the easy compounds have been done already. We have approximately 500 technical reports and looked at over 500 chemicals, and now as we get into these nutraceuticals and other things, they are posing new problems and new issues, and so what do you test?

The industry is always saying that is not what we use, we don't have that kind of preparation or this kind of preparation, and the preparation determines what the toxicity is. So that seems to be most of our challenges as we move forward with those compounds.

As far as looking at new technologies, there has been a shift away -- I think Paul Howard mentioned this earlier -- there has been a shift away from the two-year bioassay. There is a lot more interest now within NTP and outside of NTP about reproductive and developmental issues, and BPA and all of these other chemicals that raise that issue.

So we are having a lot more focus on some of those particular compounds that are more of a reproductive and developmental issue. That is not to say we are getting away from our bioassay, but we are shifting directions and doing more testing in other areas as well.

I don't know if that necessarily answers your question or not.

PARTICIPANT: Yes, I think that is where I was interested, where the methods and technology need to go. So you would say reproductive and fertility and those types of points are second in line or next in line in terms of priority?

DR. WHITE: They have become a bigger issue now. Our standard bioassay -- a lot of our new study starts have used this

paradigm of perinatal exposure so we can truly look at a cradle to grave exposure. We don't do that in our mouse studies yet, but we have moved towards that in our rat studies. There is a big push from Dr. Birnbaum to push that into the mouse studies as well.

So that has become a greater focus. In fact, if you have gone to any of our board meetings in the last couple of years, you know that the discipline leaders for reproduction and development and immunotoxicology, are starting to discuss putting those types of technical reports out as well, where they make decisions based on the data on reproduction and developmental effects and immunotoxicity, whereas we used to just make calls on cancer. So we are moving in that direction as well.

PARTICIPANT: Any other questions for Dr. White? No?

DR. SACKS: Just to introduce myself, I am from the Office of the Critical Path Programs. What I wanted to do was to just give you a little perspective of where our office stands at the moment. I think there has been some confusion in the whole realm of regulatory science.

The Critical Path Initiative was something that probably many of you know was initiated by Janet Woodcock and Mark McClelland in 2004. The motivation for the Critical Path program was the fact that there was an enormous amount of expenditure on research and development by medical product developers, with diminishing returns. The number of products that were being

approved was decreasing rather than increasing. The question they were asking with a lot of validity was whether there is some way we can employ new science and new technology to hasten the development of products and to diminish the expenses.

The program started off as a small initiative, basically to look at ways to increase the pipeline. Then over the years, it expanded. It began to draw Congressional interest. It got Congressional dollars. The project began to embrace a lot of other areas. Not only did it deal with pipeline issues, but it dealt with post-marketing safety, it incorporated the MedWatch program from FDA, and the sentinel programs; I think many of you are aware of the big pharmacovigilance program, and it dealt with the review process and so on.

Then earlier this year the advancing regulatory science initiative was launched by the Commissioner. I think justifiably, many people were confused and we got a lot of blogs on the Internet to say that the Critical Path was in critical condition and was probably due for demise.

In fact, my purpose in giving this five-minute talk is to tell you where we actually stand. Critical Path is not dead. Critical Path, at least in my view, has returned to its original mission, which is the medical pipeline. I feel we have a very important role to play in focusing on all the programs that support the development of our medical products, and that

regulatory science covers a large, different area of activities that FDA is involved in.

This was just a quick summary. We started off as the Office of Cross Cutting Programs. We began the pipeline program. As I mentioned, it began to grow, there was more funding and so on. Then the regulatory science initiative in 2009 put our mission a little more in doubt. As a result of the confusion between regulatory science and Critical Path, I just wanted to reiterate that the Critical Path should be part of the regulatory science program dealing with the pipeline piece.

What I wanted to do was just give you an idea of projects within the realm of Critical Path and some that are not. So biomarkers, modeling, data standards, trial design and strategies are all in the line of product development, and these are all programs we are embracing.

The programs that are very much part of regulatory science, but not part of the pipeline are things like post-marketing safety, sentinel, food safety, comparative effectiveness, risk management, et cetera. So I think you get the general picture.

I just wanted to finish off with two little algorithms. The first was something which is a trajectory I think many of you will recognize. This goes from product discovery up on the left there to some public health goal that is being serviced at the

bottom. As products are discovered, they go through clinical testing, phase 1 and 2 testing, phase 3 testing and postmarketing. The question is, how can Critical Path use its own tools to augment the process at various points, how do we employ new science, new information management, training, collaborations, regulations and guidances.

Phrased slightly differently, what we have done on the left-hand side of the slide are a lot of buckets of tools we have at our disposal to hasten product development. On the right we have a lot of public health goals. These are lined up and they can be changed; they line up with the strategic objectives for the agency. The question we have to ask ourselves in developing our program is how can we dip into the biomarker bucket and find biomarkers that serve the development of products for antimicrobial and resistance or for special populations, et cetera.

So as you can see, there are many different buckets our tools fall into. Biomarkers are a very important one. Modeling is another one, so is trial design strategies, bioinformatics, et cetera.

At this point I wanted to emphasize the importance of NCTR. That is pretty much a cornerstone of these predictive toolboxes we use for product development. It falls in the modeling buckets. I know a couple of folks here in the audience

have seen these slides before. Carolyn certainly has criticized my choice of the term "modeling," but I am using it in the broadest of terms here. It incorporates animal models, *in silico* models, et cetera. But modeling is something we have to rely on NCTR very much. I am hoping that during our subsequent discussions we will be able to talk about some of the more specific areas of modeling.

I think I am going to stop there and just open this up for questions at this point.

DR. AFSHARI: Thank you. Questions for Dr. Sacks? I will start off with one. Certainly when you look at the left-hand side of this slide and the various tools, you can see opportunities for NCTR and collaboration with the sciences here. You mentioned modeling, but certainly for biomarkers, bioinformatics and some of the education pieces.

We heard from Dr. Slikker earlier of the emphasis on training and education. So again, the opportunity to capitalize on some of that effort seems to be an obvious one from my view.

If you look at the right-hand side, I am looking at the special populations in pediatrics and pregnancy, thinking about some of the work being done here with the rhesus models, and the pediatric question around anesthetics and pregnancy as well as some of the DART studies. What are the other emerging areas

around special populations your office is focused on or potentially prioritizing?

DR. SACKS: There has been quite a bit effort to deal with neglected diseases. That is partly because it has been Congressionally mandated. In fact, we have dedicated part of our money to populations in neglected diseases. Those are not small populations; they are large populations, but populations suffering from diseases that are not seen in the U.S. They will be underserved by the drug development industry.

These are diseases like many parasitic diseases, leishmaniasis and Trypanosomiasis and Chagas disease, for example. That is an area of special populations that are not served in this country. In fact, it is another area where we are very much looking for support.

There are a couple of ideas we have been developing to service those areas, things like the repurposing of drugs, which is something that is very much part of the industry, but not part of FDA. That is one program we are really anxious to promote. Using animal platforms for developing some of these repurposed drugs, drugs that are already approved for other indications, is something we feel is a very fruitful area. I think that is one area we are looking at.

Obviously there are other target diseases that are of interest. Tuberculosis is another one Congress has highlighted.

It has become a big problem in the realm of NDR and XDR TB. So those are some targeted public health areas.

In terms of special populations, I'm not sure if there is any establish program in those areas other than these diseases.

DR. WATKINS: There is money appropriated for this. Does this have a physical location? Is there an office? Is there a full-time director? Are you the director?

DR. SACKS: I am the Acting Director.

DR. WATKINS: Okay, Acting Director. How many staff?

DR. SACKS: Let me just describe the overview of the program. Perhaps I should have done this in the beginning. This is called Congressionally-appropriated funds. Last year we were funded with $16 million. The Critical Path Initiative itself is an agency-wide initiative. Many of the Centers are very actively engaged in Critical Path programs.

My office coordinates that. Over and above the base funding that goes to each of the Centers to fund their projects, we have a residue of funding which we have delegated to a number of other cost-cutting programs across the agency. That included things like modernizing clinical trials under the guise of a CITI collaboration; I'm not sure you are aware of the collaboration with the CPATH Institute, but we just put out a large RFA for tuberculosis and neglected diseases, which is funding external collaborations. Those have all just recently been announced;

three million dollars were appropriated for that. Those funds have been designed for five biomarker programs and one modeling program.

So yes, we do have a physical presence. My immediate office is small as the office managing the program, but in its broadest scope, it is very large. Each of the Centers has many people working on projects that get a large amount of money from us.

DR. WATKINS: Can I just ask how much of the $16 million goes outside the FDA?

DR. SACKS: For collaborations outside the FDA, we have been mandated by Congress to ensure that at least six million is spent on external collaborations. It is not stipulated that it all has to go outside, but basically that is the general idea.

DR. WATKINS: And the Critical Path Institute, is there a formal relationship or not?

DR. SACKS: No, there is no formal relationship. The Critical Path Institute is a group of scientists led by Ray Woosley in Arizona who set themselves up to serve some of the objectives of FDA and to serve as a neutral ground for bringing together various partnerships.

But no, they are one of our beneficiaries. They have been awarded some of our money in the past. They are involved in a number of Critical Path-type projects with FDA. They are

running a couple of things like the Coalition Against Major Diseases, which is an initiative concentrating on Alzheimer's and Parkinson's disease, looking at modeling natural histories from placebo groups and trials. So that is their function. But they are not part of us at all, they are completely separate.

PARTICIPANT: Other questions for Dr. Sacks? If not, then I would like to open up the floor. We put off some of the NCTR division directors from comments here because we are also expecting you to be here tomorrow morning for comments. But, we would like to open it up for comments today because we are actually ahead of schedule.

Agenda Item: Discussion on the Need for Research and Potential Collaborations

PARTICIPANT: Our division is working with CDER to do classification algorithms for adverse drug response. So we are involved with it.

The comment of our colleague who left already, there is not enough data in that data set. It is not genotypically rich enough to identify ahead of schedule some of the adverse drug response.

PARTICIPANT: Well, it is an emerging science, and I think they are moving forward.

PARTICIPANT: Yes.

PARTICIPANT: I also wanted to respond to the question Dr. Spielberg asked of Joe Hanig which is, how do you motivate pharmaceutical companies to want to continue to do research?

I know some people at pharmaceutical companies who are working in the genomics arena, using an example of renetecam (?) with Pfizer, where an academic group looking at a clinical response of, I believe it was bone marrow toxicity, came to the FDA. The FDA mandated a label change. Then the clinicians were asking Pfizer, what does this do to my efficacy if I lower the dose for the susceptible population, and Pfizer had no response because they had no time to study it.

I know a lot of people within other pharmaceutical companies who were using that as an example to their management to say, if we don't study it that is fine, but we are putting our head in the sand, because everyone out there is studying their drug. We had better be ready when they come in with these issues.

So that was one way that people were trying to motivate within pharmaceuticals to be enabled to study drugs, postmarket.

PARTICIPANT: I think doing that type of research may discourage off-label use of these drugs, because when it comes in that way and the clinicians still want to use it, they will use it off-label and we would rather not see that happen, if possible. We would rather see a better selection of patient populations and maybe an alternative drug.

So I think we are moving forward on it, let's put it that way.

PARTICIPANT: But again, that might be one argument we want to get back to pharmaceutical companies. You don't want to do your postmarket research, but academics are out there doing it and your competitors are doing it.

PARTICIPANT: Exactly.

PARTICIPANT: And it can come back and affect your drug label, so you might want to rethink your position.

PARTICIPANT: Let me just make one other comment about that, having served on a scientific advisory board with a major pharmaceutical company in the past.

At least one big pharmaceutical company is in serious trouble. There is some concern they are going to go away. So, one has to be a little realistic when you start talking about doing all this research after drugs are out there in the real market. In my experience, right now in big pharma, which was described by Peter Hoenig recently as being in a state of apoptosis, they are really not thinking beyond a couple of quarters at this stage, for a very real reason, their financial survival.

So that is just a practical reality when you start thinking about pushing more and more of this work onto the

pharmaceutical industry ledger. It is just not going to happen, I don't think, in the near term anyway.

PARTICIPANT: I just wondered what proportion of the budget of big pharma is spent on advertising, and could they cut that out and do the studies?

PARTICIPANT: I think that is probably beyond NCTR right now.

PARTICIPANT: I realize that is out of the realm of the discussion, but it did cross my mind.

PARTICIPANT: Let me just bring together some points Paul and others made, and back to Leonard a little bit as well. One of the things on your list there is personalized medicine. One way this has been used in a positive and productive way is, identifying sets of individuals to then undergo clinical trials. I think this has been pushed forward by Alan Rose and others.

It seems like you have a chance of having a positive impact on product development for a subset of individuals that may be useful both for those individuals and for industry to be able to absorb the cost of doing a more limited trial that may have very productive outcomes. I was on the scientific advisory board for ten years. I think what he is talking about is in phase 3, looking back at that stage. What Alan was argued for is, let's get our drugs on the market much earlier, but then do it in a controlled setting, so it is like phase 3B, where it is in the

real world, real people with real diseases, real background, and it is all in Kaiser so the physician will write on the pink prescription pad. It is like a baby when it is born, it gets the genes.

PARTICIPANT: Some of Alan's material is talking about applying that to phase 1 and phase 2 as well.

PARTICIPANT: We have those kinds of clinical trials ongoing. It is in a whole new area that is called co-development, where they are developing a new diagnostic assay to look at a particular phenotype, hand-in-hand with a new therapeutic to target that phenotype in the disease.

We are doing a lot of cross-Center regulatory framework development to be able to facilitate what has been coined co-development of a diagnostic marker with a new clinical treatment.

PARTICIPANT: I stand corrected.

PARTICIPANT: We have some in our Center. I know Center of Drugs has things.

PARTICIPANT: You are talking about efficacy, though.

PARTICIPANT: But they are starting in phase one to do this co-development aspect. So we have phase one clinical trials in our Center, I know, doing these types of approaches.

PARTICIPANT: I think these personalized medicine strategies early on, because you know the target and you know the polymorphisms in the target, are great. But it does nothing for

safety. You still have to do 5,000 people to get approval for a year.

PARTICIPANT: But depending on what you are stratifying for, it could either be for safety or for efficacy, through the particular phenotype you are screening for.

PARTICIPANT: Unless we do mechanisms for those rare toxicities.

PARTICIPANT: We don't, though.

PARTICIPANT: The validation strategy for safety biomarkers is a pretty burdensome one relative to what you need for markers for efficacy. I think we have seen those cases illustrated through the Critical Path and some of the work with the nephrotoxicity biomarkers.

PARTICIPANT: I think there is no question there are great strategies to show your drug works in shorter and shorter, and smaller clinical trials, and even get personalized medicine tested to get the people who will benefit most.

But this is NCTR, toxicology. The adverse events, there has been no sign of any progress that I can see in the last 30 years, in preventing rare adverse events, the idiosyncratic variety, which right now from where I sit, the FDA is almost paralyzed in many cases because of these rare but very severe events.

So all these things that will show your drug works faster, quicker, more efficiently, and in smaller clinical trials, would have little benefit in the current environment unless you can get on top of these rare events. I have never heard anybody argue that point.

DR.AFSHARI: Dr. Sacks, did you want to add something?

DR. SACKS: I was just going to give you a historical example. Probably one of the oldest examples of personalized medicine that probably would have been very valuable in drug development pertains to Primaquine, a drug that was developed maybe 50 years ago for relapsing malarias. The dose was very low. The selected dose was limited by a very severe toxicity in a proportion of patients with hemolysis.

It was only 20 years later that people discovered C6PD deficiency was the underlying cause. Had that been known in the beginning, the drug could have been much more effectively developed at good doses for patients who were not susceptible to the hemolytic reaction.

So I think there are many examples, where if we had known up front which populations to exclude, the drug would have been developed effectively, obviously, not ideally for everyone. We tried to do that sort of characterization for people at risk for QT toxicity, for example. There are a slew of drugs which are potentially QT prolongers. My office has started getting involved

in an attempt to identify some of the genomic markers based on QT. But if those were available, it would allow us to develop products which would probably die without some sort of reliable biomarker.

Obviously they don't get at the super rare adverse events. I think that is something beyond our scope as well.

DR. KAPUT: In mouse studies for acetaminophen, in which they looked at a variety of strains. I think we do have an approach to look for rare events if we can expand our analysis of the genotype. The mouse strains give us that possibility, to at least address it. Comparative genomics *in silico* would then give us the ability to expand that into humans.

PARTICIPANT: Yes. So referring to using genetically defined but very heterogeneous populations of mice to look for that one outlier, I am a big fan of that, but in honesty if you give the mouse the commercially available 35 lines, Prozac, one strain reliably dies. So it is still an experimental approach here.

PARTICIPANT: I think it is experimental.

PARTICIPANT: You would end up killing maybe more drugs than you would save with that approach right now, but it is a very promising experimental approach.

PARTICIPANT: I don't think it is ready to say we are going to do every one like that, but I think we have to get the models like that, so we can say what the ranges of genotypes we

can look at are, what it teaches us. We can use acetaminophen as an example or something else, where you can then go from the mouse genes and pathways.

PARTICIPANT: That is something that Hesse with Pfizer and our institute is doing, looking at Isoniazid. In that case, as they generate hypotheses and genetic susceptibility across the screens, David Goldstein at Duke is doing whole exome sequencing in 40 patients who got severe Isoniazid toxicity. So he would be able to test any specific hypothesis to see if it is relevant to human susceptibility that afternoon.

PARTICIPANT: I forgot to mention this in my talk. We are working with Alan Shulby at the University of Maryland, on aspirin for platelet aggregation and looking at extreme phenotypes and what we call exome sequencing.

PARTICIPANT: Is it in mice or in humans?

PARTICIPANT: In humans. So we are actually doing this type of work now to see if we can identify the genotypes.

PARTICIPANT: Having sort of introduced this thing, I have to take the responsibility for a lot of the pushback on it. My intention really was to suggest that, in the future, as a result of doing research and applying these brand-new techniques, the new science of postmarketing predictions would emerge. But, unfortunately, I think a lot of us are considering it in terms of

regulatory things right now in the context of our present approach to things.

You really have to make a distinction. You really have to make a distinction between what we can do now with the present techniques and the regulatory actions that jump out and what will happen five to ten years from now, applying all of these techniques we have spoken about. Hopefully they are going to provide reliable tools, but we are not there yet.

We certainly should think about it. I think the goal out there, protecting five or ten people from liver transplants or death and allowing another 50 million people to use a good drug is certainly a worthwhile goal, and shouldn't be limited in the context of, maybe we are going to kill big pharma or something. I don't think it is going to happen.

DR. HINES: Just one comment on the genetically diverse strain. I think it is a good model, but I think it is going to have more application for pharmacodynamics and toxicodynamics.

I keep on being struck by the fact that what we know about pharmacokinetics and toxicokinetics is because most of those systems are post speciation; it is very, very difficult to do the extrapolation from. I don't care how diverse the mouse or the rat strain is to the human situation.

I was just involved in one with pyrethroids. The systems driving the toxicity of those in the animals are

completely different than what you see in the human, and it is all based upon pharmacokinetics.

DR. FLYNN: I also wanted to mention, I'm not sure if the SAB members were aware, that this past spring the FDA signed on to a memorandum of understanding, a multi-agency consortium called Tox 21, which is dedicated to finding early biomarkers of toxicity. I believe all the FDA centers are now involved in that.

Part of those efforts are, in fact, aimed at the idea that in many cases animals are very poor predictors of humans. You can get human-based assays, and human cells, that can be probably more predictive than the animals.

I know our Center is very deeply in it. I know some of my colleagues here at NCTR are involved in it and in CDER as well. That is something brand new since this past spring, but it is one approach that will get to this issue of identifying these toxicities very early on. I think ultimately extending this through the Critical Path Initiative to the pharmaceutical industry, and maybe weeding out the bad actors very early in the process, would be beneficial.

PARTICIPANT: Yesterday at the NTP staff meeting, it was brought up about Tox 21. I wasn't aware of this, but big pharma has donated 600 drugs that failed clinically to this Tox 21 program, along with the data packages to be opened by Tox 21, to see how predictive this Tox 21 approach is of clinical failure.

This, to me, is a remarkable step forward, saying we failed, and if you could have predicted it, to start validating these *in vitro* approaches.

PARTICIPANT: Now I am going to kill some of the enthusiasm. Chris Austin at NCGC, who has been doing a lot of high throughput testing, himself says when he gets up, most of these assays do not have the ability to metabolize the drugs being tested. Since a lot of the toxicity is caused by the metabolites, these assays are going to miss all of that.

So although a positive may mean something, we have to be aware that a negative may not mean anything. That is just to put this in perspective, because it is one unfortunate part of isolated *in vitro* cells.

PARTICIPANT: But there are some new systems coming out that do have metabolic capacity.

PARTICIPANT: There are some, but they are certainly not going to be all the different pathways and mechanisms we are looking at with all the other cell lines. So there are going to be a few cells that can metabolize, but they are not going to be looking at everything the other cell lines are going to be, or specific pathways of looking at, for example, endocrine receptors.

I was in a meeting a few weeks ago. The endocrine receptor alpha binding, for example, is not going to be done.

PARTICIPANT: Well-designed studies with mixed cell cultures could possibly answer some of that.

PARTICIPANT: The problem is that they really need to do things in 384-well plate. They need things they can culture and because the volume of the supernatant is so low, you can't put things in these plates and let them grow for five days. They need to work with very specific parameters.

At the meeting a few weeks ago, we talked about the issue. As long as everyone keeps the positives and the negatives of this in perspective, I think this is a really interesting project. But you have to keep the negatives in mind, which again is -- using almost all cell lines, because primary cells are difficult to deal with, they don't like the 384-well culture, most of these are transformed cells, and on and on and on.

The amount of discussion that goes on about the selection of cell lines is actually quite interesting. These are not always easy decisions. I just got involved recently, and I asked the basic question, when this project got started, was there a basic discussion of, are we happier with false positives or false negatives? Usually pharmaceutical companies don't want a false positive, in a toxicity assay certainly, but regulators don't want a false negative. Apparently that concept has never been addressed.

So you are trying to make a decision of what cell line is best, and people were worried about false positives. I kept asking, you are going to get one way or the other, so which way are we happier, and there is no uniform decision on that.

PARTICIPANT: But it is a critical issue in validating the qualification of biomarkers, false positive versus false negative.

PARTICIPANT: Absolutely.

PARTICIPANT: And what system you are operating in.

PARTICIPANT: Right, but I was most surprised that there wasn't some kind of general discussion at the beginning that helps drive the selection of the different cells. It is a question across any kind of assay, and apparently that was never decided.

PARTICIPANT: The cells are also genotypically different and usually aneuploid in culture. Sanger and the U.K. system, EDI, have now characterized 750 different cell lines for karyotype and, in many cases, for copy number variance, translocations, et cetera.

PARTICIPANT: They are actually aware of all that. What they are thinking of doing is, I can't remember how many cycles of testing, but they are going to try to metabolically phenotype the cells, because they knew about these various drifts also. They are going to start doing LCMS metabolomics to try to get some idea

of the phenotype of the cells. I don't believe it was with every assay, but it was with every certain number of assays.

PARTICIPANT: I was just going to try to summarize now, just to give everybody food for thought. I see a lot of interesting dinner conversations coming out of the past half hour.

Realize that for tomorrow, a main part of our goal is thinking about how the Scientific Advisory Board process can be most effective for NCTR moving forward. So as you have your wine tonight, reflect on all the talks we heard from the NCTR division directors today, which gave us a high-level, broad brush stroke of the expertise and capabilities here, the needs we heard from the Center representatives who were here from across FDA, and dovetailed and interwoven with that, the presentation Bill gave us regarding the strategic mission and the five-year plan NCTR has in place, how he is looking to evolve that on a yearly basis, and how we can best impact that moving forward.

So it is quite a lot to digest. I like how the program was set up to give us all of this information today and some time to think about it. But be prepared to come with your ideas tomorrow in terms of how we can evolve the SAB process to be most effective to support and prioritize some of the things we are hearing here, if we think those were important for NCTR to pursue.