U.S. FOOD AND DRUG ADMINISTRATION

National Center for Toxicological Research

Science Advisory Board Meeting

March 19, 2019

Heifer Village
1 World Avenue
Little Rock, AR 72202

Contents

P R O C E E D I N G S (8:00 a.m.)

Agenda Item: Welcome and Overview

DR. LEIN: Maybe we could all get settled in and get started. It's 8 o'clock.

I'd like to welcome everybody here to the 2019 Scientific Advisory Board Meeting for the National Center for Toxicological Research. My name is Pamela Lein. I am a professor at the University of California Davis, and I'm chair of the Scientific Advisory Board, and I'd like to briefly go around the table and have everybody introduce themselves, and once we've done that, we'll go and have everybody in the audience briefly introduce themselves.

So, Mickey, would you please start?

DR. ASCHNER: Michael Aschner, I come from Albert Einstein College of Medicine, Department of Molecular Pharmacology.

DR. KASPAR: Hi, I'm Chuck Kaspar, I'm from the University of Wisconsin at Madison, from the Department of Bacteriology.

DR. STICE: Hi, I'm Steve Stice. I'm from the University of Georgia. I direct the Regenerative Bioscience Center.

DR. FELTER: I'm Susan Felter. I work for Proctor & Gamble in their corporate human safety division.

DR. MENDRICK: I'm Donna Mendrick. I'm the designated federal official for this meeting.

DR. SLIKKER: Good morning, everyone. I'm Bill Slikker, Director of NCTR FDA.

DR. HINTON: Good morning, I'm Denise Hinton, Chief Scientist, FDA.

DR. RUIZ: Good morning, I'm Juan Ruiz. I'm Deputy Director for Science at CDER FDA, Office of Translational Sciences.

DR. VAN BEMMEL: Good morning, I'm Dana Van Bemmel. I'm a Branch Chief with the Office of Science at the Center for Tobacco Products, FDA.

DR. WILSON: Good morning, Carolyn Wilson, Associate Director for Research at the Center for Biologics Evaluation and Research.

DR. AUNGST: Hi, I'm Jason Aungst, Toxicology Supervisor of Division of Food Contact Notifications, in the Center for Food Safety and Applied Nutrition.

DR. ALLEN: Good morning, I'm Mary Allen, Deputy Officer at the Office of Research Center for Veterinary Medicine in Laurel, Maryland.

DR. TONG: Weida Tong, at NCTR as a Division Director of Bioinformatics and Biostatistics.

DR. LIACHENKO: Hi, I'm Serguei Liachenko, from

Division of Neurotoxicology, NCTR.

DR. DA COSTA: I'm Goncalo Gamboa da Costa, Division of Biochemical Toxicology and FDA liaison to the National Toxicology Program.

DR: WOODLING: Kellie Woodling, NCTR Division of Biochemical Toxicology.

DR. FERGUSON: Sherry Ferguson, I'm the Director of the Division of Neurotoxicology at NCTR.

DR. MATTES: Bill Mattes, I'm the Director of the Division of Systems Biology at NCTR.

DR. BARNHOUSE: Good morning, Bryan Barnhouse, Arkansas Research Alliance.

DR. PATRI: Good morning, Anil Patri, Director of the Nanotechnology Core Facility at NCTR.

DR. CERNIGLIA: Carl Cerniglia, Division of Microbiology.

DR. BELAND: I'm Fred Beland in the Division of Biochemical Toxicology.

DR. HEFLICH: Bob Heflich, Division of Genetic and Molecular Toxicology.

DR. GU: I'm Qiang Gu, Biologist Division of Neurotoxicology at NCTR.

DR. SUTHERLAND: Vicki Sutherland, National Toxicology Program.

DR. FIELDEN: Mark Fielden, Amgen.

DR. CAMACHO: Luisa Camacho, with Division of Biochemical Toxicology, NCTR.

DR. ZHOU: Tong Zhou, FDA Center for Veterinary Medicine.

DR. NAGUMALLI: Suresh Nagumalli, Division of Biochemical Toxicology, NCTR.

DR. TRBOJEVICH: Raul Trbojevich, Division of Biochemical Toxicology.

DR. FANG: Hong Fang, Office of Scientific Coordination.

DR. GUO: Lei Guo, NCTR.

DR. SCHNACKENBERG: Laura Schnackenberg, NCTR, Division of Systems Biology.

DR. SHPYLEVA: Dr. Svitlana Shpyleva, Division of Biochemical Toxicology.

MR. REYNOLDS: Jeff Reynolds, graphics, NCTR.

DR. MANJANATHA: Good morning, I'm Manju Manjanatha from the Division of Genetic and Molecular Toxicology, NCTR.

DR. PARSONS: Barbara Parsons, Division of Genetic and Molecular Toxicology, NCTR.

DR. PATTERSON: Tucker Patterson, Associate Director for Science and Policy, NCTR.

DR. THORN: David Thorn, NCTR, Division of Systems Biology.

DR. SARKAR: Sumit Sarkar, NCTR, Division of Neurotoxicology.

DR. CASON: Winona Cason, NCTR, Executive Officer.

DR. BEGER: Richard Beger, Division of Systems Biology.

DR. HE: Zhen He, Neurotoxicology, NCTR.

DR. ROSENFELDT: Hans Rosenfeldt, Deputy Director, Division of Nonclinical Science, Center for Tobacco Products.

DR. CHEMERYNSKI: Good morning, Susan Chemerynski, I'm a Toxicology Branch Chief, also in the Division of Nonclinical Science at the Center for Tobacco Products at FDA.

DR. KWAN: Good morning, Jonathan Kwan. I'm with the Center for Tobacco Products in the Office of Science.

DR. SMITH-ROE: Stephanie Smith-Roe, Biomolecular Screening Branch at the National Toxicology Program, NIEHS.

DR. OLIVERO: Good morning, Ofelia Olivero, National Cancer Institute, NIH.

DR. LEIN: Okay, I think we had a few people that walked in.

DR. ALI: Syed Ali, from Division of

Neurotoxicology.

DR. TALPOS: John Talpos, neurotoxicology.

DR. NAYAK: Raj Nayak, Associate Director for Regulatory Compliance and Risk Management for NCTR.

DR. SHI: Good morning, I'm Qiang Shi, Division of Systems Biology, NCTR.

DR. VIJAY: Vikrant Vijay, Systems Biology, NCTR.

DR. CAMPBELL: Kim Campbell, ADRA, NCTR.

MS. VYAS: Tonya Vyas, Communications Officer, NCTR.

DR. LEIN: Okay, thank you, everybody. So, I'm going to turn this over to Donna Mendrick, who will remind us of the charge to the various committees here and the rules of engagement.

Agenda Item: Conflict of Interest Statement and Housekeeping Items

DR. MENDRICK: I like the idea of the rules of engagement. So good morning. I'm Donna Mendrick, the designated federal official, and I'd like to welcome everyone to the NCTR Science Advisory Board meeting.

We appreciate the time and diligent work of our board members, for preparing for this meeting and for their forthcoming deliberations. I and the board wish to thank the FDA Regulatory Centers and NIEHS for their

participation in this meeting, and my NCTR colleagues for all their efforts preparing for this meeting.

As the DFO for this meeting, I serve as a liaison between the board and the agency. I'm responsible for ensuring all provisions of the Federal Advisory Committee Act, FACA, are met regarding the operations of this board.

Also in my role as DFO, our critical responsibility is to work with appropriate agency officials to ensure that all appropriate ethics regulations are satisfied. In that capacity, board members are briefed on the provisions of the federal conflict of interest laws. In addition, each SAB participant has filed a standard government financial disclosure report.

We have a full agenda, yet strive to ensure adequate time for the presentations, public comments, and board's thorough deliberations. This special note for all presenters, board members, and other participants. Please speak into your microphone and identify yourself since this meeting is being recorded and a transcript will be posted on our external website. Be sure to turn off your microphone after you're finished.

Pursuant to FACA, we will have a public comment period from 1:15 to 2:15 p.m. today, offering the public the opportunity to provide comments about the topics being

considered before the board today. For members of the public requesting time to make a public comment, your remarks need to be limited to five minutes. For those public commenters that have not preregistered, please notify me if you're interested in making a comment. As of now, we have no registered public commenters.

I would like to add that during presentation discussion, if board members require a greater clarification on an issue, requiring participation from attendees in the audience, they may request such information during the meeting through the chair or myself. In accordance with FACA, minutes of this meeting will be prepared, as will a transcript. Both will be posted to the website. Thus, please remember this is a public meeting.

I wish to thank the board for your participation in today's meeting. A little note, at the back of the books, if you want the books shipped to you, there's a page. Just put in your address, leave the book behind and we'll actually ship it to you instead of having you try to carry it on the plane. Thank you.

DR. LEIN: Thank you very much, Donna. So, we are well ahead of schedule. So you have a lot of time to speak, Bill. So we'll now hear from Dr. William Slikker, NCTR Director.

Agenda Item: State of the Center

DR. SLIKKER: So let me just say that I'm very encouraged to see what a great turnout we have. It's fabulous to see all the faces, both familiar and new, and I welcome you to the NCTR Science Advisory Board meeting. You know, it really is an important time for us. We do this once a year, and this one has special importance, because it had to be shifted about three months downstream because of the untimely death of President Bush. It allowed us to cancel the last meeting and move it to now.

But I'm really appreciative of everyone who has come, and I also want to say that it's going to be a great opportunity to review the progress of not only NCTR, but FDA, over this last year plus a few months.

The thing is that this review is very critical to us. It's not only important because we're getting the latest scientific input of course from our Science Advisory Board members, but also because we're getting input from our colleagues from other centers of the FDA. And this is a critical sort of marrying together of the cutting-edge science with the needs of FDA, and that's what this meeting is all about, so I really appreciate everybody taking part.

I also appreciate, of course, Donna and the entire team, who put together these presentations, to make

them available to everyone. What we want to do from these presentations, of course, is get your input. And what we want to do is ask questions at the end of each one, have you consider those, and certainly give us immediate feedback, but also if there's feedback that you want to give us later, please also push that forward, as well.

It's very important that we have these discussions over these topics so that we can move forward in a very coherent way in which we're combining both the latest science as well as the input and needs of the agency in which we function, which is the FDA.

So, let me just give you a few information tips about this. Obviously, we're not on the NCTR campus. We are in Little Rock, and we're still about 30 to 35 miles away from the actual campus. For any of those that haven't been there, we'd be happy to arrange a tour. But it's much more efficient for us to meet here in this nice facility and be able to do this so we don't have to transport people and utilize a couple hours of our precious time each and every day. So this way, we can meet here very efficiently.

But the campus is huge. It's -- you're talking about 550-some acres, you're talking about 30 buildings, you're talking about 1.2 million square feet of floor space, and it all belongs to FDA. It not only belongs to

FDA, but it's all managed and regulated by FDA, and that means that we can make alterations in the grounds and the structure, put in new buildings, and we don't have to ask anybody except where's the money coming from. Because GSA is not involved in this. This is just FDA control.

This is great, and we have a real great group of engineers. They're on campus that report to headquarters that maintain and take care of these buildings, and always advise us about how we can do new buildings, which we like to hear about. So it's a fantastic campus, and those that haven't seen it, I certainly welcome you to come out and visit with us.

The thing is that the mission and vision of NCTR has really evolved over many years. This particular facility is over 40 years of age. It was initially determined by executive order, but it fills a certain niche that's sort of been altering and changing and improving over the years. Right now, our main goal is to generate data for FDA decision-making, and that's been sort of a constant, but I think the other half of what we do is really focused on new technologies, and building those kinds of approaches that could be useful into the future. So we have really done much more than what we were originally designed to do, and it all is in the direction

of improving background information, decision-making tools for the agency of FDA.

So this is our structure, and I won't go into great detail on this, because you're going to be hearing from each one of these groups, but I think the important thing about all of this is that we have a chance to talk about these research divisions, and this is really the critical part, of course. We're all about research, we're all about generating new science to support the agency, and so you'll hear from the division of microbiology, genetic and molecular toxicology, in more detail in the next day and a half after this full meeting. Division of biochemical tox, division of systems biology, division of neurotox, and division of bioinformatics and biostatistics. It is functioning under a whole bunch of offices here. I won't go into great detail, but this management is really minimal. We're talking about somewhere around 10 percent of the total population is in these boxes, and you know, some 85 to 90 percent is here, where it should be, and that's where we do our research.

But it is very efficient to have this management that's so competent right here on our campus to handle all the interactions with other parts of the agency and the world, as well as interactions between our divisions, and

also maintaining the structural part as well as the part that has to do with budget et cetera. So that's all managed that way.

So what I want to do is just talk a little bit about our staff. We have a really exciting and informed and accomplished staff, and what you can see here is that we do have 290 or so FTEs and another 103 contractors. It's actually a bit larger than that, but these onsite contractors are not quite the same as people normally think about contractors. These are individuals who oftentimes have been working at the center for 30 or in some cases 40 years. It's the management changes perhaps every five years, because these are usually five-year contracts and they are competitive of course, for management. But oftentimes, what the management finds is the best people to do the job are there right now, and they continue to work for different management schemes over the years.

So these are although they're contractors, they're really part of our family and we owe them a great deal, because they have tremendous institutional memory and are so useful to the agency getting their job done. These are individuals that work in nutrition, that work in pathology, that work in animal care, that work in the facilities, maintain the facilities. These are individuals

that really are the structural background for NCTR.

And then ORISE. This is our program so that we can train individuals from both the United States and around the world, and we have many individuals who are in the training position and we'll talk a bit more about that later. The idea, these are very critical for us to be able to train. Many of these individuals go on to work in industry or other government agencies. Many of them end up in White Oak or at CFSAN, carrying out duties within the FDA, but the role here for us is to train these individuals in usually a two- or three-year program. And we have many of those, and that program is continually refreshed on a continual basis.

So, what about the research goals? Well, and you know, certainly to advance scientific knowledge is a key part of this, and really, it's to support that whole area of personal, animal, and public health. It's broad, because it reaches every part of FDA's responsibility, and all the individuals that are here to represent the various centers of FDA and ORA, they recognize that we work with them on a daily basis to advance their knowledge and understanding so they can move things forward.

They have input from many different sources, but we feel like that we're one of their internal sources

within the FDA to provide this information to them. Also, of course, one of our goals is to always continually enhance these collaborations. As you know, with any large organization like the FDA, there's turnover of staff, there's new challenges that arise, so we need to keep in constant contact with our collaborators in the other centers and ORA aspects of FDA so that we can stay current and make sure that we're solving the needs that FDA has.

And then of course the global outreach we feel is very critical, and the reason for this is that, as you're well aware, in terms of pharmaceutical ingredients, there's a large percentage, well over 50 percent, that comes from outside the United States. So we want to make sure that what is imported in the United States is of high standards.

Also, food sources, as you realize, 30 or more percent depending on what food area you're speaking of, is imported from outside the United States. So we want all of our colleagues that are working in other countries that are providing a lot of these materials to the United States to use the same principles and standards and approaches that we use within the FDA. So we feel that training and interacting globally is very critical to succeeding and providing the safety to the American public.

Now, what are some of the accomplishments for

this period of time? I'll just go over a few examples. Obviously, we're not going to get everything. At any one time, we have approximately 200 projects that are moving forward and being actively pursued at the NCTR. So I'm just going to cover a few of those examples. But, I mean, the main thing of course is this idea of improved scientific partnerships within the FDA family, and we think this is a very critical point that we pursue.

Also the idea of just advancing the regulatory sciences in general. As you know, there's always new approaches, new opportunities arising, and NCTR by being involved in that process of developing some of those technologies of exercising and testing those technologies and understanding how they apply to FDA needs or fit for purpose is something that we do on a continual basis, and actually about 50 percent plus of our resources goes into that sort of cutting-edge idea of what the future's going to be, or tools and approaches that FDA will use. Then also we spend time advancing our global outreach and, for the reasons that I already mentioned, this is a critical part of our accomplishments as well.

So, one of the things that we want to talk about is interactions with each one of the centers, and there's many, many examples here so we just picked out a few we

thought would be of interest. But certainly, Center for Drugs, we have many different areas we're working on. The opioids continues to be an issue, but those that got a chance to listen to the commissioner at the sort of town hall meeting yesterday, he mentioned that the opioid crisis will remain on top of the list, one of the top of the list items for the FDA. We feel this is really important, and we are developing some methodologies along that line to hopefully be more efficient in that area.

The pediatric anesthetic area is something that we've been pursuing for the last almost 13 years now. This is in conjunction with CDER, very closely linked to them. Many of our collaborators are there at CDER. We just had a meeting yesterday, actually, on this very topic. And the idea here is that we want to have the safest kind of anesthesia possible for children, so how can we get there as a nation and as an FDA, and that's what those studies are pointed toward.

In fact, there was a warning that went out a couple of years ago that long-term anesthesia, we're talking about over five or six hours of anesthesia, and certain developmental stages, sensitive stages of development in humans, could be considered an issue and a warning went out based on all those studies that have been

done between CDER and NCTR over the years, as well as others from academic centers.

And then of course, the monograph, which is an activity that we're doing in conjunction with CDER where we have a memorandum of understanding is important because it focuses on a variety of issues that we think are important ingredients in sunscreens, ingredients in other kinds of antiseptics, et cetera, and is broadening out to even more areas of interest. So we do work with them to provide literature searches and review, and help them write up different aspects of monographs that can be useful to them.

So then with the Center for Veterinary Medicine, we have the opportunity to work on antimicrobial resistance and the human microbiome. This is really important, because this area has really blossomed, as you know, in the last five or ten years. The understanding of the microbiome actually has been within our division of microbiology for many, many years. You'll hear about that later. But the idea is that how do we apply it toxicological assessment is really where this group is pointed, and how can we use this information to improve safety assessments of FDA-related compounds. So we're really happy to be working with CVM and others within FDA on that issue.

Then the Office of Women's Health is one in which we found a really good set of collaborators within FDA, and certainly here precision medicine has come up because we can work with human populations through universities and clinical centers, and have been focusing on this, for example, this idea of the triple negative cancers that oftentimes are seen in mammary cancer and how it may be afflicting more African Americans than other populations. So there's a lot of interest here, but at any one time we may have two or three or four or more projects going with the Office of Women's Health, and as you know, they've been a tremendous funding source for us and others throughout the agency over the years.

And then of course, you know, public workshops dealing with such things as sequencing quality control. You're well aware, I'm sure, that the Division of Bioinformatics and Biostatistics has really been sort of a driving force behind quality control for not only arrays, but now next-gen sequencing, and this work which really covers all of the centers of FDA is moving forward to make sure that we know how to interpret and use next-gen sequencing data to its maximum.

Then the Center for Tobacco Products, we really sort of pride ourselves on being the in-house, inside FDA

wet lab for Center for Tobacco Products, and we really appreciate their support over the years. It's been tremendous. The interaction has really covered a broad area, including inhalation toxicology, and this is both done in vivo and in vitro, so it's a whole new area of in vitro exposure of cells to various kinds of tobacco products in the vapor phase.

We also have a variety of alternate models that have been developed along with them, and biomarkers of course of toxicity are very important here, and looking at hazard. Then modeling and predictive toxicology, we have a tremendous modeling capability here with pharmacokinetic modeling and other kinds of modeling approaches. Jeff Fisher is helping to lead up that organization, but many more are involved in that, and that activity is very critical both from the exposure point of view and the toxicity point of view. And then as I mentioned, the pharmacokinetic analysis after exposure to various constituents of tobacco smoke is very critical to the FDA, in general, and something that we could work with CTP on delivering that bit of information.

So along with that, I just want to go over a few other accomplishments. Certainly, NCTR is all about developing partnerships and I think you're aware of that,

not only partnerships of course with the other centers of FDA and ORA, but also with outside entities. And over the years we've had collaborations with the National Institutes on Drug Abuse, with NIEHS, with NIOSH, with USDA, EPA, you know, you name, it we've been involved. The Army from time to time, DoD. But this one, with the National Center for Environmental Health Sciences and the National Toxicology Program, of which FDA is a full member, has really been noteworthy, and that's because this relationship now is over 24 years of age. It's one of the longest lasting memorandums of understanding that I'm aware of. It's also one that has far-reaching implications, because this is a way in which FDA gets resources to do the critical work they need to get done, and so we're very happy about that relationship.

Over the years, you know, there's been some $220 million-plus that have come into FDA as a partnership with the National Toxicology Program of which FDA is a member, but the idea is that that money has been used to solve important issues. And certainly one of those that has been on the front burner, and now the studies are completed and the final reports and publications are going out, is on BPA. Before that, furan, and also melamine/cyanuric acid. Many different projects have been tackled in conjunction

with both CFSAN and CVM over the years.

Also the idea of understanding more about potential toxicity of aloe and aloe vera, especially since as you're probably aware if you've been to health food store, that you can buy a gallon jug of this to drink if you want to. I'm not sure why, but people do it, and we wanted to understand if that was an issue or not. And those studies are nearing completion as well.

Then brominated vegetable oils, the list goes on. Nattokinases, you can just see that there's a lot of different assays. Triclosan with CDER, and then work going on of course with airway models with CDRH together with NTP. So all in all, this income source is very important to the agency to solve important problems that cut across various agencies, and of course is all motivated and controlled by the National Toxicology Program, which we have some really good members here today.

So, moving on then to projects in general at NCTR. You know, one often thinks about NCTR as it was first created. It was to do long-term low-dose exposures, and some of you might even remember the idea that there was an EDO1 study, effective dose of 1 percent, a study that was done many years ago, one of the largest studies of its type ever completed, and it was done at NCTR.

But since those days, there's been a broad amplification of the projects that NCTR is capable of completing. And this sort of gives you an indication that a lot of the work that we do at NCTR is developing new and alternative methods and that a lot of it has to do with pharmacokinetic modeling, biological modeling, using various kinds of systematic approaches in the bioinformatics area, and also a lot of in vitro approaches, cell culture approaches as well, and stem cell approaches, using both animal and human cells. So it is quite amazing that really there's sort of now almost the balance is tipped a little bit in favor of nonanimal studies compared to animal studies. But the idea is that we're still doing both, and we're improving each and every one of these where we can.

So what about some of the accomplishments and the different kinds of approaches out there? You see by this laundry list that we are quite broad in this, and that this gets to the point, you know, using imaging instead of having to do serial sections or that sort of thing of tissues. We can use imaging. We have two different MRI machines, both narrow and wide bore, as well as two PET machines that allow you to get to information about biochemical effects in living organisms or in cells, and so

these are available now as well as the modeling capability I mentioned and the microbiome that we mentioned, and this whole idea of applying it to precision or personalized medicine.

Then also on this list of course is the regulatory science training that I mentioned earlier, so key to us to train those students for the future, both for individuals that stay within the FDA and those that stay within the United States, but also, though, those that perhaps go back to their country of origin and do great work in other countries to bring up the standards around the world.

So let me then just turn to a little bit more detail on some of this work that we're doing in the bioinformatic area. One of these areas that's really been pushed forward very nicely by our Division of Bioinformatics and Biostatistics is this review to research and return, R2R program. And we found this to be very popular, especially with CDER, but also with other centers of FDA in trying to get the most efficient software on the desk of the reviewer. How can we make the reviewers job be accomplished faster, more effectively, more efficiently, and software packages that they can use that they really want to use and know how to use are critical to getting

their job done quickly?

Many of these kinds of work done by other review centers has a timeline associated with it, and so we want to be able to help them move that through more quickly. And certainly this collaboration with CDER on the DASH system, the Data Analysis Host System has been key to this, and what we're finding is that other centers want to join in and take part in this as well, which we really appreciate and want to include everybody.

So you know, updating these systems is really important and what we find is that the collaboration directly with scientists here at NCTR they know how to improve the program, they know how to write the right code, they know how to get that code in a position where it can be useful with the FDA. I think that many within FDA realize the importance of that, and having that done sort of in-house rather than contracting those kinds of things out. So I think it's been a really successful program and one that keeps building.

The other area that I just wanted to mention briefly is precision medicine, and of course this cuts across several different centers of FDA. We've done a great deal of work in this area developing new biomarkers to push forward precision medicine. We've also led

activities having to do with entire special issues of well-known journals to sort of emphasize this area, and I noted yesterday that Scott Gottlieb, our commissioner, had Rob Califf on the FDA site to discuss this whole area of precision medicine, along with our new principal deputy director, commissioner I should say, of FDA, Amy Abernethy, but the three of them were discussing this idea of solutions in precision medicine and how that area is so critical to FDA moving forward.

Then the artificial intelligence area. By now all of you in this room know that artificial intelligence and deep learning methodologies have actually been around for a long time, but they've been captured under this rubric of artificial intelligence. But it is an area that of course is very important to FDA and to NCTR, in particular, and so again, Division of Bioinformatics and Biostatistics and others working at FDA have really been pushing this area forward for many years, but now it seems to be gaining new energy and enthusiasm, which we appreciate.

So let me then just sort of get near the end here and talk a little bit more about the area in the international scene, and we think this is critical for the reasons I already mentioned about training individuals in

other countries to be having the same sort of general principles and approaches that we have within the Americas, and especially within the FDA, and so we've been able to pull together with help from several different commissioners over the years, this group that's called the Global Coalition for Regulatory Science Research, and I'm going to emphasize research, because we're not about changing regulations or policies or inspections, we're talking about the research side of regulatory science, and we're talking about agencies that are well known to many of you.

These range from everywhere from those agencies that are like the FDA in Japan and Brazil, over in the EU, which as you know is 26 or maybe 25 countries now, depending on who you listen to. Also, Korea, of course, China is one of our newer members, Argentina, Canada, Singapore, I mean this is those people who are movers and shakers in regulatory science are on this list, so we're very happy about that, and we keep growing it, and it looks like we may have interest now from also India and other countries, as well.

So what have we been doing in this group? I mean, one thing that we hold an annual conference. So there are four working groups within this, one on

bioinformatics, one on nanotechnology, one on emerging technology, and the fourth one is more on training. So all these areas are moving forward, and so we rotate the theme of the global summit on regulatory science to fit the theme of those working groups.

So we just held the one in China, Risk Benefit of Dietary Supplements and Herbal Medicines in the Era of Data Science. This was held in Beijing. Our collaborators there did a great job as local organizers, and we had a great turnout with about 15 different countries involved, and it was fabulous to see people come together on this important issue with many representatives of course, and presentations from other centers of FDA.

Then the one that's coming up, a little advertisement here. This will be the ninth global summit on regulatory science, and it's going to be focused on nanotechnologies and nanoplastics, and so this area which will be September 16 through 20 in 2019, so it's coming up this September, will be right there in the EU in the beautiful lake country of Italy, and JRC, the Joint Research group will be ones that help us do the local organizing. They're great partners in generating this area, moving it forward. So that'll be coming up, and again, we already have speakers lined up from other centers

of FDA to talk about these exciting and new areas within the regulatory sciences arena.

So let me just finish up then by talking about some of the changes that have occurred in NCTR, and actually when I had a chance to visit with the commissioner just last week, he mentioned, well, how's the session planning coming along, and I had to report that we're doing pretty good in that area. So one of the things that we're doing is sort of finetuning some of the divisions. Now, all the divisions except for one and we're still working on that one, do have either a deputy director or have a branch structure within the organization. That gives the chance for more training of individuals in management and also gives the chance for any succession planning that may be coming our way.

I have to say that when we talk about management at NCTR, it's a little different than perhaps other organizations. Basically, if you're selected to be a division director or a deputy division director or branch chief, that you carry on your research at 100 percent and you sort of do the management on the side, because there's nothing like leading by example. So everybody is under the same rule set, and our program, which either involves a peer review of the science and/or perhaps some select

groups like Senior Biomedical Research Service, they are competitive based on research and you do all that and then you do that very well, and then you also get to manage people, in addition. But we have lots of people within our hierarchy to help you manage and a great HR team, and management team at the NCTR-wide level, and they help you get this done. But that's the way we do work at NCTR. We make sure that we lead by example. And research and science is what we lead by.

Other appointments is that I'm very happy to announce that Tucker Patterson -- Dr. Patterson has moved into the Associate Director for Science and Policy, and he has been so busy because it just is a very important job and one in which he is capable of handling, but it certainly has increased his workload as he takes on these new duties. Rajesh Nayak has moved into the job as Associate Director for Regulatory Compliance and Risk Management, has great experience and background for this, and is doing an excellent job there in that position. And then of course Brad Schnackenberg, who many of you know is sort of the liaison for the Center of Tobacco Products and that work, also is now the Associate Director of Office of Science Coordination, which is a group that really runs the backbone of animal care and a whole host of other

activities associated with maintaining research at NCTR.

And then just a couple of transitions in the Division of Bioinformatics and Biostatistics. They've moved to a four-branch structure which is really working out very well, and the Division of Neurotoxicology, I'm proud to announce that, after the previous director stepped down, that now we have Dr. Sherry Ferguson, who's now the leader of the Division of Neurotoxicology, and she's doing a fantastic job. Again, doing the research and also doing the management as well. So we're very happy with these transitions that have occurred.

So, just to cover briefly a couple of sort of new proposals, although these now have a few months if not more time on them actually, but the analytics and imaging working group was the main group that was reviewed last year at this very meeting as a subcommittee, and we'll be hearing more about that activity, not only at this meeting but also later. So we're very happy with that activity and that focus on analytics and imaging, moving forward.

This really has to do with the whole idea of big data, how you manage large datasets that are generated, either through nanotechnology, through various kinds of high-level imaging approaches and/or high-level mass spec kinds of approaches, and how you work this altogether with

the databases that you have to maintain and organize and keep track of. So that really focuses on that whole area that's so critical for these large datasets that are being generated by science in these days.

And then also the one on perinatal health center of excellence. Now, I'll give you a couple words about that. Why do we want to move into this area, and this was really determined several years ago, but the idea is that we felt like a virtual center of excellence that really focused on this perinatal period would be wise. One of the reasons is that this whole area seems to be understudied, and there's many unmet needs.

It's been difficult over the years, of course, to do clinical trials when you're talking about pregnant women or children, especially preemies, and so we felt this area needed to be enhanced, and also it's something that was available to be enhanced across all the centers, and not just one or another, but all of them could be involved in this process. And as it turns out, NCTR has a long history in working in perinatal health, especially in developing animal models, et cetera.

So we went through several steps, and the funding was placed in the budget. As you know, the government cycle, it takes about three years to get something

initiated and finally funded. We had to wait a bit longer than that. We had to wait until after the shutdown, until finally the budget was approved. But by golly, there it was. We got the FY19 budget request, and we got the funding for our perinatal health center of excellence.

We didn't, of course, sit back during that period of time. We started six or eight months ago, to actually engender interest in this area and actually get submissions put in for funding. We had over 22 applications that came in, a real enthusiasm group from all the different centers in ORA, and the idea was that we would be able to evaluate those. So we set up committees that were across the different centers of the FDA. We had a committee that sort of helped with the process, to get out the word about what was going to be asked for in these proposals, and then we also had a group that were the leadership council that were the ones to evaluate the proposals. They had representatives from each center and from ORA.

In starting up that process, we were able to get proposals in months ago, long before we had the budget, but we thought it was important to get a good start on this. Like I said, we were able then to evaluate 15 proposals -- well, total of 22 we evaluated. Fifteen looked like they had promise, and 14 of those were actually funded just two

weeks ago, and so now these are moving forward with funding for those 14 with the 2019 budget coming through, and so they're on their way. They're going to be developing data that we can celebrate in the near future. So we're very excited about that, and all the collaborations we have with the various centers and ORA to make that happen.

So, you know, what can this provide to us? Well, we're hoping this approach, which does cover everything from cells in culture to alternate models to modeling to bioanalytic approaches, information sciences, omics of various kinds, bioinformatic approaches in general -- they're all covered, and human studies. So we've got everything from cells in culture to human studies that have been funded of those 14 that are moving forward. So we really think they can to apply broadly to FDA needs.

So finally, I just want to leave you with some questions, as most of the speakers will today. They really focus on, you know, sort of where we're going in the future. That's what this meeting is all about. I had fun telling you about what are the things we've done in the past, but what I'm trying to do is stress where we want to go in the future, and we need your input to make those kinds of decisions.

So really, it has to do with how good are the

animal models? How can we test the animal models and the new tools that are coming along to make sure that they're really going to be effective for FDA? What are some of the examples of current regulatory approaches that can be useful to looking at alternative approaches? And also, how do we evaluate these models? The thing is is that fit for purpose is really an important theme for FDA, and there's many different purposes, depending on whether you have regulations that relate to food or relate to medicines or biologics, et cetera.

But the point is that we need to make sure that what we develop with the other centers is something that's going to be useful to them. And then, how can some of these in silica approaches really be useful? We already have a lot of examples of that, but we like to make sure that we're evaluating all the opportunities. Then what are some of the additional needs to really extrapolate between the in vivo and in vitro approaches, and can that be enhanced using pharmacokinetic and modeling approaches, et cetera?

So, those are some of the questions that I put out to all of you to think about, and we appreciate your input on those. So with that, I'll close, and open it up for brief questions. Thank you all very much for your

attention.

(Applause.)

DR. LEIN: Thank you, Dr. Slikker. Does anybody in the audience have any questions? Anyone from the Scientific Advisory Board? I've just been reminded the audience is not supposed to ask questions, but the Scientific Advisory Board? Do you have any questions you would like to ask of Dr. Slikker?

DR. STICE: Bill, thanks. Very impressive. Steve Stice from University of Georgia on the Scientific Advisory Board. A couple questions and a comment here. Bill, in the numbers that you ran through, are those numbers up in any category, down -- can you give us a sense of where the center is going as far as number of personnel in those various three areas that you mentioned?

DR. SLIKKER: Right, so the deal is is that the numbers of individuals at NCTR has been relatively stable over the last several years, and that's because our budget has been relatively stable. That's good, because we know with a lot of federal agencies, the budget has been going down. However, I must say that NCTR's budget has not been increasing at the rate of FDA's budget, so this is a concern for the future. As a matter of fact, if you look at the numbers, you know we're probably in the range of

just keeping up with inflation, maybe, maybe not. So it is something where we'd like to see the opportunity for growth to keep up with the needs of the agency, and we're hoping that in the future that we might be able to add some numbers to those so that we can keep pace with the rest of the FDA.

DR. STICE: So that the number of ORISE are about stable as well, or going down?

DR. SLIKKER: It's stable, I would say, but part of it's because we really have gotten some help from some of the other centers who, say, like in the bioinformatic area that they appreciate our work so much that they're willing to support ORISE directly. They'll work at NCTR to get the product they want for use within their center. So this has been helpful to help maintain the numbers. But as you know, all those positions are temporary, and rightly so. They're training positions, but it really is something critical that for the growth of FDA that NCTR be a partner in that growth.

DR. STICE: And that as you mentioned, many of those are foreign students that maybe are going back to those 15 different countries that you talked about, that you're helping train. To me, that seems like another aspect of what you're doing is potentially training not

just through conferences, but also training through scientists that can go back to those countries, which may actually have a bigger impact in the end than a two-day or three-day conference type of thing. I don't know if that's something you track or something you want to comment on.

DR. SLIKKER: We do, actually, and when you visit NCTR, you can see our wall of fame, which is the listing of some 1,300 individuals that have been trained at NCTR either three days' or three years' worth of training. It is pretty amazing. It hasn't been updated recently because it's a static on the wall to make it impressive, but it's more than 1,300 at this point in time.

Actually, at any one time, we may have individuals from various parts of the world on the NCTR FDA campus, and it's not unlike us over the years to have trained individuals from over 50 different countries. It is an international training zone. We think that's really critical, because all the world has safety issues, and all the world produces some products, many of them at a high rate, and we need to be making sure that the principles and approaches they're using are consistent with the FDA needs, and so that's one way to do that.

And you know, we are facing some trials in this regard, because of the new regulations about individuals

need to be in the country three to five years to be able to be reviewed and be able to come and work for the FDA and many other federal agencies. So, the issue is going to be how do you make up that population that you're losing access to. That is very key and one of the challenges for us right now.

So one of the things that we're doing, and Winona Cason, who is our executive officer, and Robby Robinson, who's our HR person, have been partnering with folks that are responsible for recruitment and that sort of thing in Washington, in the FDA offices there, and trying to figure out ways in which we can enhance the number of individuals coming from the state of Arkansas into training programs, and also the rest of the United States in the training programs, because obviously that target pool now is going to be more important to us than ever before.

So this is really key, and so I spent a lot of time when I am at conferences or interacting with my colleagues at university saying, hey, do you have any good students that might be interested in doing a postdoc at NCTR, because this is going to be a lifeline for us and one in which we have to work very hard at filling this gap. We've always gone after students, the best and brightest from all around the world, and now we're limited in that,

and we really need to look to the United States under these new regulations to make sure we can fill those important needs for the FDA.

DR. STICE: Impressive, yes. And the question on the shift to 48 percent nonanimal or in vitro, I'm assuming, type of studies, how big a shift is that? I mean, is that -- it looks like that's the majority, I mean, 48 percent of activity, is that a big shift or a gradual shift?

DR. SLIKKER: No, Steve, it's an incremental change, and it's been happening over many years. But if you think about the importance of our bioinformatic activities, if you think about the importance of the in vitro models, if you think about the importance of our modeling capability, if you think about the importance of human studies, many of our studies are done in conjunction with medical schools and other clinical facilities where we're using either human cells or human tissues or in some case, we're collaborating on actual human studies done on those clinical campuses. So it is a combination of things, methods development, in vitro systems, as well as human studies, that make up that now sort of majority of activities at NCTR. So it is a shift that's been occurring, I think, at an appropriate and sort of a slow

rate in that direction over many years from what we were 47 years ago when we were doing mainly just one study, one big, big study to now where we have 200 studies running at any one time.

DR. STICE: Just this last comment, the DASH system to me seems really important, I hope that it is really important. It seems like, you know, the age of all these new sponsors and everything coming in and having a system that can be used by the reviewers in this whole area seems really important. I commend you for doing that work.

DR. SLIKKER: Well, thank you Steve, and you'll be hearing more about that when various people talk about that issue in the near future, just in the next little bit.

Yes, Mickey?

DR. ASCHNER: Yeah, thank you very much -- very nice presentation. Michael Aschner, SAB.

Great work, and I'm happy to be on the board again. You mentioned a couple of threats, basically, the training, the way I perceive it, and the budget. Are there any other big threats to the NCTR?

DR. SLIKKER: Well, you know, I think that you mentioned the two that probably are on the horizon right now that are gaining a lot of -- taking a lot of our time to try to deal with in a very collaborative way with the

other centers of FDA, as well as reaching out to others that can help. But I think that in general, our role is to continue to stay closely linked to the other centers so we can help them solve any issues that may come forward.

So collaboration and communication are key items here, okay, and so the closer that we can be to the other centers that would hopefully appreciate our work and certainly have demonstrated the appreciation of our work over the years, that close linkage and ability to communicate directly with them is a key feature, because people within the FDA are very busy. Those that are making the decisions as reviewers have timelines associated with those documents. They have to work in a very constructive and effective way, and they don't really have a lot of time to reach out and you know go to a seminar here and meet so-and-so there or come and visit us at NCTR.

So we have to find ways to take the information to them, okay, and to make sure that they realize that if they have a question, we can help them answer it in a collaborative way where they're full partners in this relationship. So I think the communication and ability to let people be aware throughout all of FDA what some of the capabilities, opportunities, and interest there is within NCTR to help them move forward -- we need that bit of work

done on a continual basis because, as I mentioned, there's always turnover in FDA, there's always turnover in any organization, and so you have to continually renew these connections, build these connections, and make sure that people are aware of the opportunities, because that's what we want to be. We want to help them solve their issues at every level of the FDA.

DR. FELTER: Susan Felter, SAB. So, Bill, my first question might tie into what you're just talking about, the needs for the other FDA centers and opportunities to partner, I think it was a little over a month ago that the FDA announced the formation of -- I believe they're calling it the Botanical Safety Consortium, and I'm wondering if that's something that NCTR either has a role in or envisions a role in, given that you guys have done research -- in fact, you have some ongoing research with the aloe that you mentioned. My other question is whether you've been impacted by changing policies on stem cell research, if that's had any impact.

DR. SLIKKER: Let me start with the interaction with the botanicals, and the interest in dietary supplements is sort of a global term, we have great connections there, and I'd like to invite up Goncalo, who's our NTP representative and liaison in this area.

Goncalo, would you just come up and say a few words about this particular question if you would please, about the interaction with some of the other centers in this regard?

DR. DA COSTA: Yes, so everything is in motion at this stage, and there's two separate components. There's the Botanical Safety Consortium, which is a consortium encompassing members of the government where the National Toxicology Program is taking an organizing role at this stage, so encompassing folks on the division of the NTP at the NIEHS, and mainly folks at the CFSAN, and then also encompassing partners in the industry.

There's also going to be a botanicals safety working group within the agency, but which is just an internal group. But there's a lot in motion here, so as you were mentioning, it's been one month since the commissioner has made the advertisement, so you should be hearing more about these new programs soon.

DR. SLIKKER: Thank you, Goncalo. Now I was so interested in his answer, I forgot to remember the second half of your question.

DR. FELTER: The second question is just whether there's been any impact on research at NCTR from the change in policy on human stem cells.

DR. SLIKKER: Well, not at this point in time, because obviously we're not doing some of the things that others may be doing with stem cells. We're mainly using them as models. But at this point in time, we're still able to work with stem cells. Now, the cells that we work with, of course, have to follow certain characteristics. They have to be available to the public or the researchers at large. So they have to be commercially available, and so this is something that is critical to us, and so there's plenty of sources now, and so that really hasn't been a limiting factor as I understand it.

DR. LEIN: Okay, thank you. This is Pam Lein. In the interest of time, I think we'll move on to the next presentation. Thank you very much, Dr. Slikker.

Okay, so our next presentation will be by Dr. Steven Stice, who is chair of the subcommittee review for 2017.

Agenda Item: Subcommittee Review, 2017

DR. STICE: Good morning, everyone. Steve Stice, SAB member and the co-chair on the subcommittee for work on reviewing the analytics area. My co-chair in this area is Mickey Aschner, and also present during those times was Susan as well -- Felter -- that contributed to this report. Also Greg Lanza, who is a former SAB member, also was a

primary reviewer on this. We also had outside reviewers from Richard Corley as well as Patrick McConville, as well.

So, our 11-page report is in your packet of information, and I have no intentions of reading the whole thing to you, but you're welcome. I just want to hit some highlights on what we were asked to do, what we found, and maybe some thoughts going forward. Of course, any of the other people on the review committee are more than welcome to comment on this.

So just some high level thoughts from the committee were that, you know, we were asked to review some cross-cutting sciences, and that was not only one area but multiple areas from nanotechnology core facilities to bioimaging capabilities to bioanalytic imaging, imaging large, small, databases and modeling, which is a broad swath of activities that are going on in the center.

These are really valuable resources for the FDA. That's one really important area we were really impressed by the leadership, the collaboration, the excellence in the science that was being conducted in these areas, and most impressively is the accomplishments that they've been able to make with the resources that they have had.

It's a unique interdisciplinary approach that has been -- and the matrix is unique as well. So we strongly

recommend that this unique resource be preserved and supported in future years. We really think the strengths, as I mentioned previously, are in the collaborative relationships and the interdisciplinary programs, and again, the general responsiveness to the needs of the FDA in general and their focal points are of high relevance.

There is obviously with all this broad base of analytics, there's a need to continually assess where we are, where the NCTR is, making sure that it's fundamentally sound research, and that we recommend that we continue at the director's level, continually review these areas and assess that needing improvements in certain areas, as the science advances, as the areas of interest change in this area.

But in general, it's a really excellent multi-research area with being able to conduct this and limited personnel budgets that may be level are shrinking, and so with that you have to really be strong in looking at the areas of strength, and continuing excellent research in those existing areas, and then in the future incorporating these emerging technologies as they come about, as these groups are currently doing.

In our charge letter, we were asked to cover three particular areas, and those are how best to organize

these activities for NCTR and the rest of FDA. Second, what is the expertise that are missing? What physical plant changes do we need in those areas? Third, what might be on the horizon in these areas that we should explore. So we did our best to try and address these areas as a subcommittee.

The first one, how best to organize these activities at NCTR and the rest of FDA, is really a difficult one and one that I think is important to address. We continue to again suggest that the research be responsive to the projects and need of different centers in the FDA. Those are really important things that they must do. But at the same time, that presents some difficulties in conducting long term strategic planning and can be difficult for organizational structures. We acknowledge that, and I think the group is doing as best as they can in these areas.

One of the things that was a recurring theme for our report throughout was the fact that we were concerned about the staff and the numbers in particular areas, that these projects can be slowed or maybe some of the projects can't even be initiated. I know that that's a continual area of focus for the leadership in the center. In particular, I think one of the things that was pointed out

that staff with the image analysis expertise and experience are a critical resource, and there needs to be more people in the NCTR with that type of focus.

We did mention that there might be opportunities for cross-training of individuals. In our minds, I don't think we were thinking that everybody should be trained in mass spec and NMR and analytics and modeling. What we were saying is that there are opportunities for collaboration that may be again getting out of a potential for silos building, to try to get more people going across different labs. Not everybody can be an expert in everything. We acknowledge that. We just think there's more opportunities to better train individuals by giving them opportunities to train in multiple labs going forward.

Again, some of the recommendations, the flat organizational structure that the report we think is fairly flat already, but continuing to go down that path. Facilitating knowledge by sharing, pooling resources. Again, having direct connections with teams and labs, and that's going to the cross-training potential, going forward.

So, in the next question that we wanted to address was a review and recommend changes to core areas of expertise in physical plant. One of the things that's

quite evident from the presentations that were given to us is there is cutting edge technology capabilities and equipment, and that goes to the credit of many people, but particularly we wanted to point out that the nanotechnology program was an excellent program with world leadership under Dr. Patri.

We think that there's a lot of hands on as Dr. Slikker mentioned, hands on research as well as instruction and training in these areas. We think that the nanotechnology core clearly has the equipment and the know how to address most of the issues that are clearly on the FDA's review horizon that's equipped with vital instruments ranging from field flow fractionation, FLPC, numerous types of mass spec, dynamic particle size analysis, outstanding electron microscopes including standard transmission scanning EMs, cryo-electron microscopy and low voltage SEM and 3D SEM. We think the plan in the past and the future as far as building the physical plant is excellent, and excellent equipment.

Again, it's been very productive, but we see it being handicapped at some level by turnover of key personnel and the fact that we have many postdocs that come in that have projects that they may then leave, and then those projects may be hampered or slowed with the ability

to hire new postdocs and get them up to speed in a rapid fashion. So being able to recruit people we think is important to be considered going forward, as an area of places where we could do more.

The FDA reviewer issues relating to nanotechnology products or products incorporating nanotechnology, whether it's food or medically oriented, will increasingly depend on NCTR for training, consultation, and independent testing and evaluation. The demand on these facilities will not decrease but only increase, going forward.

Other -- we did look at imaging assessment, as well. The current focus on neuroimaging and neurotoxicity and imaging platforms are appropriate, we thought. We thought development of new and novel imaging biomarkers for neurotox is a more challenging endeavor and just something that you'll have to continually address. Without having a cyclotron or a local producer of short-lived isotopes is an issue that has to continually be on the mind of the staff and the leadership of the center.

We do want more focus on trying to improve the impact. The imaging team should be viewed as a critical core capability, directly connected with multiple specific NCTR projects, and focus on applying key adverse responses

or disease pathways and environmental capabilities. So that's a large ask, a large area that needs to be continually addressed, going forward.

Then the next one was the electron microscopy core. We thought that was extremely impressive facility, multiple state-of-the-art instrumentations, and applications for the NCTR and broad agency. From the MRI perspective, we thought the NCTR instrumentation again is outstanding. The results have been really excellent, and we hope that more will come from the staff in these areas.

Let me jump ahead. There's a lot of information on that that was provided by Greg Lanza, one of the committee members, that can be read.

Some of the comments on common issues, on operating and maintaining these instrumentations. Maintenance agreements are expensive. I don't know how you get around those expenses, but trying to continually be innovative and trying to figure out how best to use resources for those purposes is important. You have to maintain those pieces of equipment, and that's going to be important.

We said that, again, limited term employees like postdocs can be really problematic at times. It's inevitable loss of their corporate, quote unquote,

corporate memory, and can be disruptive when those postdocs leave, so we hope that there's capability to get more long-term staff in those areas.

The nanomaterial assessment was also conducted. I'm not going to hit on those.

I did want to say a few things on the image analysis modeling and computational analysis. We think that this area has demonstrated good productivity across numerous relevant and high priority projects. The use of these resources is highly project-specific, and the potential exists to create a broader and more far-reaching and higher impact resource with existing technologies and software and personnel. So we encourage the group to reach higher. We commend them for what they've been able to do on productivity, but continue to expand in these areas would be really helpful for the FDA.

The structure of the groups involved in data analysis and image analysis should be such that they are directly or regularly connected with labs that can benefit from these resources, and we think that that's happening, seeing the response from the group. We see a number of activities in this area that we think is responsive to our questions and observations in this area.

And then lastly, what are the areas of emerging

needs for the NCTR? Where should they be explored? Given everything that the center is doing already, we want to be cautious in how broadly and thinly you limit or deploy your staff in these areas, but we see some trends that are happening that were outlined in the report. Suffice it to say that we think that the trend in nanoscience, there's a number of different biologics area from vaccine development to a number of areas including things like exosomes, macrophage, phagocytosis, a number of areas that could be explored in the future in the biologics area that is clearly outlined in our report.

We also think that labeling of biologic cells and nanoparticles may be really critical technology to focus on in order for better understanding of biodistribution, off-target accumulation, safety clearance, residence times for the immunotherapies. These are all areas of need, we believe, and could be an area of further study for the centers and analytic area in the future.

So just wrapping it up, and I'll open it up to Mickey or others, in summary, I think the nanotoxicology core has a really high appreciation for what has been achieved in terms of their development of that center and the people that are associated with that area. We think the whole area of analytics is an area of high need, for

the broad FDA, and should be a continual area of focus for the NCTR. We think the use of seminar series should strengthen areas of interest, with invitees from outside NCTR, particularly those of other federal agencies with overlapping and/or complementary expertise is an area of potential action. I think that's been initiated, and we can always hope for pilot funds for essential training, as well as enhancing collaborations across campuses, and I think continually soliciting ideas from the broad campuses of our centers, I should say, of FDA is important for input into areas of need and this area.

With that, I'm going to ask others, Mickey, if you have any further comments. What did I miss?

DR. ASCHNER: Michael Aschner, SAB. I don't have any other comments, Steve. I think you did a great job. My recollection is that for the discussions we came to a consensus that you can't be everything to everyone, that you obviously have to be, you know, focused where you decide to focus on. You may need some additional personnel. Steve mentioned those areas.

I think probably the most important thing, given that, you know, there are other centers that I can think of that are doing some similar things, that you have to focus on those areas where you feel there's added value to what's

already being done. And I think this can be done through cross-fertilization between NCTR and other FDA centers. And I think you're doing it to a great extent, but critically, I think the focus must be maintained.

DR. LEIN: Thank you. Susan, did you have anything to add?

So one thing that seemed to be a recurring theme when I reviewed this was also the idea of needing to maybe increase the number of personnel with the expertise, which your ORISE program potentially could be leveraged to do that, to bring in people that could help build that expertise. But also there was a recurring theme of image analysis, and really needing to maybe develop a more broad impact image analysis core within NCTR, rather than having it focused in small areas.

So thank you very much to the members that prepared the report. It was very comprehensive and easy to read, and I appreciate your efforts. Thank you.

So I think at this point, Donna, we're ready to take a break.

Oh, we have to vote, sorry.

So we have to vote to accept the report of the Scientific Advisory Board. So, this is a vote of the Scientific Advisory Board.

So all in favor, raise your hands.

(Show of hands.)

So it's unanimous, thank you.

Okay, now Donna, we are allowed to take our break. So we are scheduled to reconvene to hear the response to the review at 10 am.

(Brief recess.)

Agenda Item: Response to Review

DR. LEIN: This is Pam Lein, SAB chair. I just wanted to let everybody know that there'll be a slight change in the schedule for this afternoon. It turns out that there are no public comments. So you actually start the NCTR division directors' overview of research, or continue, I should say, at 1:15. So we'll, again, start with the division directors' overviews at 11, go to 12:30, break for lunch at 12:30, and then at 1:15 we'll come back and continue with those overviews, with the goal of maybe getting out of here a little bit earlier, and no, those of you in the afternoon do not have longer for your presentations. Sorry.

The other comment that I've heard is that the people in the back of the room are having a hard hearing those of us at the U-shaped table here when we speak. So we need to put our mouths pretty much right up against the

microphone. So, just a word going forward.

With that I'd like to ask Dr. Schnackenberg to commence with the response to the review. Thank you.

DR. SCHNACKENBERG: Okay, thank you very much. This is actually going to be a co-presentation between myself and Anil. So I'm going to cover the imaging technologies, the modeling, and the imaging needs in terms of IT support. And then Anil will respond to the nanotechnology.

As you heard before the break, rather than our usual review, the divisions that we go through every year, the subcommittee was tasked with reviewing a broad range of technologies. So these are across a number of different divisions at NCTR. This included the MRI, PET, CT, MALDI imaging mass spectrometry, a little bit of modeling by Dr. Jeff Fisher, and then we had Ted Bearden, who presented some of the needs from the IT-type standpoint, and then as well, of course, the nanotechnology.

First of all, I'd like to say, again, we really appreciate the careful review and suggestions by the subcommittee provided in the report, and we really appreciate the time that they took to give their expert analysis and suggestions. We know that they did put a lot of time into this report, and as you saw in your binders,

if you had it, it was a very comprehensive report focusing on the various areas that we asked to be evaluated. We do take the advice of the subcommittee very seriously and will consider these comments in these areas in order to focus the needs on what the FDA programmatic needs are.

Steve mentioned before the break that there were some common themes. So just to go over those again, and this was throughout all the different areas that we presented to the subcommittee. One of the common themes that were identified included the cross-training and core imaging facility, and this was noted before the break, as well. It would be difficult to expect to train somebody in all these diverse technologies, including the EM, mass spectrometry, MRI, and expect them to be proficient. However, it may be possible to train someone in common overlapping areas, and this option will be explored as we move forward.

We are trying to make some progress in terms of the infrastructure needed to support an image repository and software, and I'll address this in a little bit as well.

Another common theme was adding to existing staff. Three areas that could benefit from the additional efforts include the recruitment of individuals with

expertise in the technologies. Postdocs, which was also noted as well earlier, so we want to look at postdocs that are well-suited to work on our specific projects. Staff that handles the data storage are sufficient, but additional training and infrastructure may be needed moving forward.

In terms of outreach, we do have a number of ongoing collaborations with multiple groups, and we're constantly continuing those efforts to kind of bring these technologies to NCTR and across FDA and in academia. While we have our ongoing collaborations, we're constantly looking for new collaborations with those people.

The specific areas that were reviewed, again, include the imaging assessment. So this is the MALDI mass spectrometry, the MRI, PET, CT, image analysis, modeling, and computational analytics, and then the nanotechnology and nanomaterial assessment. I'll kind of cover those first two bullet points, and then Anil will come up and address the nanotechnology.

Imaging assessment in general, one comment that was made in the report was that cross-center and cross-FDA collaboration should be encouraged to meet the FDA regulatory needs, and this, again, will help to develop analysis tools, and more specifically, provide molecular

probes for positron emission tomography, which was noted, again, before the break, since we don't have the capability onsite to create those compounds.

In terms of biomarker translation, the subcommittee did note in the report that efforts should be made to translate T2 magnetic resonance imaging from animal models to human, and Dr. Serguei Liachenko, who is in the audience today, is preparing a letter of intent to the biomarker qualification program at CDER to consider T2 MR imaging as a qualified biomarker of neurotoxicity in preclinical context of use. So stay tuned, that is being prepared. This will provide guidance on how to continue the program, and, again, bridge that methodology from the animal models to a clinical setting.

In terms of imaging processing and analysis, it was noted by the subcommittee as a significant challenge to increasing the impact of imaging at NCTR, with needs for image co-registration capabilities between platforms emphasized. We are in a unique position at NCTR that we have all these various imaging technologies, and so if we can figure out how to co-register these images, we're going to have a whole breadth of information that will really help us understand toxicology issues and potentially disease issues, as well. We do agree that this capability

would make it better to assess and understand adverse responses or disease pathways.

It was also noted that additional computing power and storage will be needed, in terms of the division of systems biology. We've also recently purchased a Bruker ScimaX mass spectrometer for imaging. So this is going to be a higher resolution imaging, so we are going to have even more larger data files with this instrument, as well, so that's something to be considered.

In terms of the modeling, the PK/PD, Dr. Fisher did appreciate the comments in support of the committee towards his modeling and simulation efforts. The committee did note, and it is agreed, that there is a lack of strategic thinking about modeling and simulation, so this needs to be addressed moving forward, so that we can better suit the needs of FDA.

In terms of imaging tools, we do appreciate the recommendations for improving the repertoire of imaging tools, management, and storage, which are common issues, again, among all the imaging technologies that we presented. We will continue to work with the research laboratories to determine the current and projected storage requirements.

In terms of this, Ted Bearden and his group did

request from the various users. Information included the estimated size of imaging data to be collected over the next two years, so this is in terms of gigabytes, terabytes; vendor or commercial software applications that will be needed to acquire, view, and analyze images. They wanted to know where is the imaging analysis done? Are you doing this at a desktop computer, is it a server, high performance cluster, other places? Are the images typically analyzed one at a time, or can this be done in batch fashion? And any other relevant information.

Ted has received some feedback from the groups and will continue to pick their brains and see what is needed over the next couple of years. But given what he's been told so far, they are addressing the data storage issue, so the external bandwidth has been increased to 10 gigabytes. Additional storage has also been purchased. It has been budgeted for general purpose graphic processing units. Currently they are evaluating cloud storage costs and the feasibility as available to FDA.

Again, they're also engaging the research staff to understand storage requirements, so as I mentioned on the last slide, what volume of data do you anticipate, what software are you using, where is the software available from, because that will obviously have to be evaluated,

whether it can be used on the FDA systems, what hardware, what's the analysis workflow? They've offered to actually send people over to the labs so they can see what goes on from your image acquisition through the processing stage, so they can really understand what happens and what the sizes of the various data are. Then evaluating image repository and analysis applications. So I think that that is all I have. Do we want to ask questions now, or wait until Anil is done with the nanotechnology?

DR. LEIN: Maybe we'll take the questions now for the imaging. That's a good idea. We have plenty of time.

Any questions from the SAB regarding the imaging component, or response to the review on imaging?

DR. ASCHNER: Michael Aschner, SAB. I have one question. I think one of the comments was that it would be nice to have co-registration of different images, and maybe I missed it, but I don't think you mentioned it. So what are the plans there?

DR. SCHNACKENBERG: For the core? Anil, are you addressing this in your portion of the talk? No? Just the core for the imaging.

DR. ASCHNER: Are there any plans for co-registration. PETs, MRI --

DR. SCHNACKENBERG: Oh, co-registration. I'm

sorry. There are plans for co-registration. It's just a matter of what software we need to use, but like I said, we have the unique capability that we have all these various technologies, and we would love to get studies together that look at PET and MALDI imaging, perhaps, maybe PET and MRI, and so it's a matter of what software needs to be used, and so this is maybe somewhere where we need to kind of find groups that are doing similar things and find out what they're using.

DR. ASCHNER: I think, again, it's going to be very important, because the kind of findings that you can put together is going to be significantly stronger if you are able to do those kinds of things. And it's only a question of getting the right software, because you are doing already all these modalities.

DR. SCHNACKENBERG: Exactly. So it's a matter of the software and then putting together the correct projects to do that, but we're, like I said, uniquely suited to do that. I don't think anybody in FDA has all these various capabilities that we do, so this is a place, I think, where we can really engage FDA and provide them with information that they cannot get elsewhere.

DR. LEIN: Actually, a lot of academic institutes are doing co-registration routinely, so there are a lot of

groups out there that have -- a lot of it is self-developed software. It's not commercially available. UC Davis has a very large, active program on that right now. You could reach out to Simon Cherry or Abhijit Chaudhari, and they'd be happy to work with you on that.

The other comment I would make is that we have found, because we also have multiple modalities that we're using within our imaging group at UC Davis, and one of the tools that's been most effective for developing shared resources is a working group. So we bring together a working group, monthly, just to share common best practices, and that's been incredibly helpful for developing shared resources. So just something to consider.

DR. SCHNACKENBERG: Definitely.

DR. STICE: Steve Stice, SAB. To that point, I guess, the other question that I would have is are there activities with other FDA centers that you can collate the best practices in these areas, and is there an opportunity? Because we understand the options may be limited, different, for the FDA, versus our universities.

DR. SCHNACKENBERG: Right. I'm more on the MALDI mass spectrometry side, and in terms of that at FDA, I think we're the only ones really doing that. But we do

have good outreach with other collaborators. There's somebody at Department of Defense who is doing a lot of MALDI imaging and a lot of academia and pharmaceutical, so we were able to, at least with the MALDI mass spec, present a workshop last week at the SOT, and to bring together kind of that group. So it might be worthwhile to pursues those arenas and kind of develop a working group out of that. If Serguei wants to try and address the MRI, would be happy to let him step in. But in terms of the expertise for the MALDI imaging, I think currently we have it, at FDA.

DR. LIACHENKO: This is Serguei Liachenko. I'm running the MRI facility at NCTR, and, yes, I could just confirm that what we are doing, it's probably the only place at FDA, so there some imaging capabilities at CBER, I know, but in terms of co-registration, I'm doing it routinely to co-register MRI to MRI images. We are working on picking up this co-registration of MRI with other things, like histological images, which is very, very challenging. There's a PET-CT co-registration going on all the time in our place, but it will require a little bit of coordination with the help of this new proposal of a shared bioanalytical imaging capabilities. But we have some tools, we have some experience, and I think what we are doing in NCTR is kind of the best practice we do at FDA

right now. That's my opinion.

DR. LEIN: Are there any other comments or questions from the SAB for Laura? Okay.

Thank you, Laura.

DR. PATRI: Thank you again. We'd like to thank the committee for doing an in-depth job with the review of the Nanocore, and providing their advice on how to move forward with the current core facility. I should say I also chair the nanotechnology taskforce in the Office of the Chief Scientist, so we do collaborate with other centers. The taskforce is composed of members from each center and office ORA at FDA.

We meet every month to figure out what is coming, what are the current challenges, and how to address those challenges, either through cores funding, which is research projects, or through internal research, if there are immediate challenges that we need to address. One area that we are investing heavily is on standards, because we cannot, as you know, we cannot do every research project on every emerging area of nanotechnology. But if we collaborate through the consensus standards, use ASTM, so an industry that can come in and we can have a significant impact on the FDA work.

Again, I would appreciate the comments on the in-

depth evaluation and recommendations, and I'm going to go through some of the highlights from the report and address the best I could.

The subcommittee advice is on three areas, mainly the electron microscopy, laboratory needs, the staffing, which is a significant need, and the Horizon scanning advice for the Nanocore on what is emerging and what we should consider.

The electron microscopy facility at the Nanocore has state-of-the-art equipment. We have a couple of transmission electron microscope, scanning electron microscopes, low voltage electron microscopes, and one special equipment that you have seen last year that Angel presented at the review, which has microtome built into a scanning electron microscope so that we could get three-dimensional information at high resolution, either in cells or in tissues.

As was presented, again, last time, and you reviewed, is one of the main challenges is that once you get these huge datasets, the personnel required to analyze that data and that is something we are lacking. Most of the electron microscopy labs in the country have two sets of people, one that do imaging, the other set of people who do image analysis, because this is huge data, the software

is nonexistent in this new area, and so we have to collaborate. I will just briefly show you what we are doing in the in-lab area in terms of collaboration, because we cannot recruit the half a dozen or so people who can do the image analysis on these datasets. Then also I will briefly talk about the horizon scanning advice.

We see nanotechnology is now merging with emerging technologies, whether it is 3D printing or other kinds of modalities, other kinds of applications. So it is difficult to catch up with everything that is coming through, but we are trying to do our best in keeping up with this.

Again, this is a comment from the subcommittee review about the excellent resources that we have, and then the storage and the software capabilities that are lacking, analytical capabilities, and personnel. We appreciate that review and comments, and so we certainly cannot bring in all the personnel that are required to do the analysis, but one thing that we are doing and this was suggested, is to collaborate with other facilities that have those kinds of capabilities. One area, or one lab, or one center, that we talked to in the previous years is the Advanced Biomedical Computing Center at the Frederick National Labs for Cancer Research, where they have all the electron microscopy,

optical, fluorescence, and animal imaging facilities, MRI, CT, PET, ultrasound imaging, and the challenges are the same.

But the ABCC, the Advanced Biomedical Computing Center, has more than 60 people that do the image analysis at NCI. So it's best for us to collaborate with them, utilize the software that they have developed, and maybe set up some combined postdocs to have, or transfer, that expertise, so when we acquire the images then they can help us with the image analysis. This is something that we are pursuing, so we can have the software -- hardware, certainly, we can buy, and we have already bought the hardware -- but then image analysis expertise that is needed in the new area. So we are pursuing this.

You may have seen this slide before. This is now a couple of years old, a 2017 publication on the nanotechnology submissions to FDA. Again, this is published in Nature Nanotechnology. My colleague Katherine Tyner from the Center for Drugs did a review of the drug product submissions containing nanomaterial. On the graph on the left, what we have done is 40 years of review of the products containing nanomaterial. Until 2015, the survey was done internally. There were close to around 350 product submissions. These are not all INDs, so the blue

bars are the INDs, which are investigational new drug submissions, so these are from preclinical, getting into clinical trials, and you can see those are gradually increasing. So the new products are coming through.

But some of them are ANDAs, or these are the generics, the green ones are the generic products. As you can see, more recent years, we see more and more genetic products in the area of liposomes and emulsions where these are traditionally research done many years ago. But since then, in the last couple of years, you can see we are close to 800 product submissions at FDA. That data is not included here. And those are close to 60 NDAs, the drug applications, and so we have 60 products, and then also the ANDAs, these are generic products.

So if you look at the kind of material, because the other thing, we have a lot of labs, a lot of equipment, at the Nanocore, but then where do we invest our resources, with the limited staff and research projects that we can do? So most of the, or one third, of the products that are submitted are based on liposomes. Then you have, again, one fourth of the products are nanocrystals. These are the products that are ground to the small size, emulsions and micelles and polymers. These are all soft material.

So nano, most people think of as hard gold or

silver particles. Those kinds of particles are used in devices area, if you look at the Center for Devices, CDRH, submissions of products containing nanomaterial, they contain titania, they contain silver, they contain cobalt, chromium, those are the metallic kind of nanomaterial that are included in the devices area.

Not only do we see the increase in the number of submissions, but we also see the complexity of these nanomaterial-containing drug products. So we see more complex multicomponent products, for example, with a targeting ligand or multiple therapeutics attached to them, and so one area that we are exploring or projects are more centered around the liposome area, where we still have challenges, even though they have been approved. These slight changes to the physicochemical characteristics, slight changes in the surfaces, will significantly change their immune recognition, biodistribution, because most of these formulations are intravenous administered. Fifty percent of them. So that's where we are, some of the investments are in that area, and the personnel.

New areas of emerging needs are, as the assessment continued, the nanomaterial physicochemical attributes, and how they influence the quality by design and how they impact the biological response for the safety

or efficacy.

So we are currently pursuing two main or big projects. One is in the liposome area, to look at multiple generic drug products that have been approved, and then the differences that are in the public domain, that these products have in clinical trials. And also on the ligand targeting. So when you go to more complex submissions, with an antibody or a small molecule targeting, how do we know that those things exist? What is the activity of those ligands, how many ligands are on the surface? These are not easy questions to solve. We still take the risk of approving based on the synthesis, the safety and efficacy data that the sponsor submitted, FDA and CDER and CDRH, but we need to learn more about those, so some of the -- at least one significant project is on that area.

The other two, macrophage phagocytosis, which is common for a lot of nanoparticles because of their immune system recognition, reticular endothelial system uptake. The nitric oxide production assay. As I mentioned, one area that we thought we could contribute and have more impact is in standards development. So we are doing collaborative consensus standards development through ASTM E56 committee on nanotechnology. The ISO/TC 229 on nanotechnology, ISO/TC 24. These are the standards bodies

where we can collaborate with industry and academia to bring the consensus standards that FDA can recognize, and then it makes it easier for industry to come through those submissions, through those standards -- it'll be easier, faster review process.

These are all suggested by the review committee, the new areas of emerging needs, including nanomaterial-based vaccines, immunotherapy, complement activation, again, we collaborated with Greg Lanza a few years ago on complement activation, and generic biologics and exosomes. Again, these are all emerging and we are planning to develop a complement activation assay as a guide, standard test method, so if you know the standards area, if it is a test method, then it has to have a precision and bias in the measurements.

So it is one thing to have analytical HPLC method, where you can have very precise measurement, but when it comes to a biological assay, in vitro assay, those are very difficult to do interlab studies to come up with precision and bias in the measurement. So, in those cases, we can develop guides and we can do this, we have been doing this with ASTM. Part of the Nanocore is dedicated to developing standards in collaboration with and support from the National Toxicology Program that funded this work, so

that we have significant impact.

The assays that I mentioned before are currently test -- these are called work items at ASTM. Then as recommended, we still didn't get into the vaccines area, immunotherapy area, and generic biologics. Again, biologics are, technically they are not considered as nanomaterial, but then certainly if there are biologics such as fragments or antibodies conjugated to a nanoparticle for targeted drug delivery systems, those are something that fall under within nanomaterial area in FDA.

So we'll consult with the product centers on the emerging challenges, and we can do this very effectively through the nanotechnology taskforce. We meet every month, and this is one area that we have been discussing and NTF decided, the taskforce decided, that one of the areas is standards. That is something that we are pursuing.

Staffing of Nanocore, this is also the SAB subcommittee recommendation. They observed the transient nature of postdocs. The market is very hard for nano, even now, and so the postdocs that come in, they get excellent training in the Nanocore facility, we have some of the best equipment in the country. And I don't say this lightly. We do have really good equipment, lots of labs. This is a collaborative facility between Office of Regulatory Affairs

and NCTR. But the postdocs that come in, they usually get another job within one year, one and a half years, and that is, that has been a problem. So the corporate memory is lost, as Steve Stice mentioned, and so one area that we are considering is to at least bring in a few new permanent staff members, maybe technicians and staff fellows that can continue the projects, that can have the corporate memory, so that we don't lose the knowledge that we gained through the postdocs. It's good for postdocs. I can boast of all the postdocs that came through my lab and then went into industry, other centers at FDA. But then the projects were slowed down once they leave.

Again, thank you for all the recommendations, and we will prioritize the projects based on our discussions with other centers through the nanotechnology taskforce. Then maybe bring in a few permanent staff. The extended collaborations with other government agencies does happen through the National Nanotechnology Initiative and the National Nanotechnology Coordination Office. I serve on the NSET and NEHI subcommittees on behalf of FDA, and so we talk to other agencies, both regulatory agencies such as EPA and research agencies, NIOSH or Consumer Protection Safety Commission, and other agencies, so we have common areas, common challenges, that we are facing based on

nanomaterial. We don't have to do what other agencies are doing, we don't need to replicate, but this is where the coordination occurs, and then come up with challenges that FDA typically is facing and try to answer some of those questions.

Again, I appreciate the input that you have provided, and I'll be happy to answer any questions you may have.

(Applause.)

DR. LEIN: Thank you very much. Any comments or questions from the Scientific Advisory Board?

DR. STICE: Steve Stice, SAB. Thanks, Laura and thanks, Anil, for a great report. Anil, can you expand more on -- you mentioned several times this taskforce, but is this taskforce charged with doing something other than just trying to help each other? Can you expand on more what the taskforce does?

DR. PATRI: The nanotechnology taskforce is part of the Office of Chief Scientist, and it is composed of members that are nominated by the center directors from each center. We meet every month, and the charter for the nanotechnology taskforce is to look at FDA challenges in this new emerging area. It was started in 2006, 13 years ago. Then there are multiple areas, so there is a line

item funding that came from Congress that is part of the taskforce, so we provide funding, these are called CORES grants, Collaborative Opportunities for Research Excellence in Science. These grants are funded in nanotechnology within FDA. That's one part of the task of the taskforce.

The other is coordinate within the agency on the emerging nanotechnology-based challenges. They establish the core facilities, and this NCTR core facility is part of that. There is another core facility, which is in the White Oak campus, that is part of the CDRH Office of Science and Engineering Labs, so that campus, mostly, utilizes that core facility. Establishing the core facility, conducting research, regulatory science research within FDA, so this is something that we try to coordinate within the agency on a monthly basis.

But extramural coordination and collaboration. So we have a formal collaboration between NCI, FDA, and NIST, the three agencies, in nanotechnology. This is a memorandum of understanding which still exists, which is still valid this day. This is to bring the data from the nanotechnology characterization lab, which did preclinical assessment, which they continue to do, bring all the data into FDA in a confidential manner, take that, and provide training to reviewers. That's another area. You do all

this research, but then how does it affect the review of the products coming through?

So we provide the training to reviewers, that's another charter. So the Nanocore at NCTR provides training to the reviewers at FDA, and then we take it to the White Oak campus, we do sometimes at the White Oak and sometimes at the NCTR Nanocore. So far, more than 120 reviewers have been trained through this training program so that whatever we learn through the research is now shared with the reviewers so that they can ask appropriate questions.

These are some of the work, and then of course the engagement, both outside the FDA with other agencies and also international engagement.

DR. STICE: One of the best ways to cross-fertilize across centers is to exchange people for a month or two months between core facilities. Is there an opportunity to do that with postdocs or staff, that they could go somewhere else and if not, I think that would be a great thing to discuss, those potential opportunities.

DR. PATRI: Thank you, that's a great idea. We didn't explore that option yet. But it is, other than the three-day training, this is something that we can explore and ask other centers if they would like to send their scientists and staff for a more extended period of time,

one month or three months, so we can have more center-specific projects that we can pursue. Thank you.

DR. LEIN: At this time I'd like to open up questions or responses to the members that are representing the different centers of the FDA. Any questions, comments?

DR. WILSON: Hi, this is Carolyn Wilson from the Center for Biologics. I just wanted to also thank the committee and the NCTR staff for the thoughtful report and echo a few points that at least are relevant to our center, that I thought really resonated with me, anyway, which is for us, cell therapies, as you obviously know, are really an emerging area. Biodistribution and how to track these cells in vivo is a really important area for us. So I appreciate the review indicating this as an important area of investigation in the future.

I also really appreciate the concept of a core facility for imaging and the idea of a working group. Last year, we actually tried, through the senior science council, to develop an informal working group for imaging, and I know that NCTR participated in it. Unfortunately, we sort of lost -- we didn't quite have the bandwidth to keep the momentum going, but I'm trying to get that reenergized so that it's actually not just a working group within NCTR, but an agency-wide working group, because we do a lot of

different types of imaging modalities also in our center, in CDRH and other places. So I think there's a lot of opportunities for better information sharing and understanding capabilities so we can also collaborate and not duplicate, and all of that.

That's it for me, thank you.

DR. SLIKKER: I'm Bill Slikker, NCTR. Thanks, Anil, and I think that in addition to reaching out to the other centers, which obviously you've done through the taskforce and through our continual sharing of protocols and research with them, is the outreach through the Global Summit for Regulatory Sciences, where you've been able to lead for the last several years as sort of the fourth or third rotation in meetings, which are nanotechnology based. There's one coming up here soon, as I mentioned, in Italy, with the drug research consortium, which is a representative of the European Union, as you know.

But Anil has reached out to many different countries and just recently received some high praise from officials from USDA and other locations within the U.S. government for his outreach to India, and the fact that they have taken on new guidances that are very much similar to what is here in the United States and in Europe when it comes to nanomaterials, and as you know, nanomaterials are

produced all over the world. Many of them are produced outside the United States, but to have a handle on the standards that we need to make sure that those nanomaterials are similar across various countries, and that when we import those at great numbers from other countries, that we understand the characterization of those is key. So Anil has helped leading that forward for the agency as well.

I will say that at these global summits we always have good representation from the other centers of FDA, and the last one that was held at NIH in Washington, two and half years ago had a great input from all those centers, and especially our colleagues from the centers that are very active in this area of nanomaterials. So we appreciate that collaborative approach, we appreciate the training that you're bringing to the agency, but also the training that you're bringing to the rest of the world so we can live in a safer place. Thank you.

DR. PATRI: Thank you, Bill. If I can quickly comment on that. I forgot to mention the progress that we made, I should say, Angel, who heads the electron microscopy facility, he's a cryo-electron microscopist, and they are very few and far between. He developed a cryo-imaging standard for liposomes using cryo-electron

microscopy, and then this recently became a standard at ASTM. It takes a couple of years to take a standard that goes through the consensus process, and so we appreciate his support and his involvement in that.

The global summit, one thing that was requested through these interactions is that you have excellent resources at FDA, but in our countries, we don't have the bandwidth to do nanotechnology but we see these. Can we send our scientists to FDA, can you train them? That's very difficult to do, to bring in a lot of people into FDA, there are logistic issues.

Instead, what we did was to take our training to the other countries. So we provided the nanotechnology training to Health Canada, so the Health Canada and Canadian food inspection agency, there were 50 people, along with my colleagues from the nanotechnology taskforce. And also, we did the same thing with India, because India has the largest production of generic drugs that come into the United States, and the capacity-building is one area the Office of International Programs is interested in.

What resulted from that is a nanotechnology guidance that came out of India, which is similar to the guidance that we have at FDA. We shared our guidance documents with Indian regulators, and that resulted, these

just came out earlier this month, that they publicly released. So these global interactions are really helpful, and the global coalition for regulatory science research and global summits that we organize, they are very useful.

The next one, as Bill mentioned, is on nanotechnology, nanoplastics. As you know, nanoplastics are the emerging challenges that all across the globe are felt, and then so we felt that's one area that we would discuss about the global challenges and then come up with the areas of research for nanoplastics.

Thank you.

DR. LEIN: Thank you. Are there any other questions or comments around the table?

I'd like to thank Laura and Anil for a very thoughtful response, and good lunch to you. You have some challenges ahead of you, but well worth taking on.

With that I think we'll move into the overviews from the NCTR division directors. The first presentation will be from Dr. Beland from the Division of Biochemical Toxicology.

Agenda Item: NCTR Division Directors: Overview of Research Activities

Agenda Item: Division of Biochemical Toxicology

DR. BELAND: First, some of you have the old

program. Goncalo Gamboa da Costa was supposed to give this presentation. So, I am not Goncalo, okay. All right.

We were asked to follow a prescribed format. So I assume you're going to see slides like this throughout the rest of the presentations. Anyway. This sort of describes the division. We have 27 permanent people, our staff fellows, who I consider permanent people, but they're generally staff fellows because of visa issues. We have support scientists who are fulltime government employees. We have an administrative staff. And then we also have ORISE.

Over the years, we're fairly stable, and this has been one thing I've learned about NCTR, we don't have a lot of turnover. I'm going to lose a couple of people at the end of the month, one Xiaoxia Yang is going to go to CTP. I'm sorry to lose her, but she's going for good reasons. Allen Triplett is going to go to the EPA. We've been able to recruit to backfill. We've been very lucky to do that.

But as far as I'm concerned, a huge issue is this inability that we've been faced with in the last year or two to recruit foreign scientists. I think it's a horrible, horrible mistake. I think it's a detriment to science in the United States, and I hope it gets corrected soon, because while we've been able to go out and find

people within the United States, I think having foreign scientists, foreign-born scientists, foreign-educated scientists, has made a tremendous difference at NCTR, and particularly the division that I'm associated with.

As far as outreach, we collaborate with all of the divisions at NCTR, with the work that we do, so we're very dependent upon biostatistics for example. We have a long history of doing genetic toxicology, which is Bob Heflich's division. Microbiology, we're heavily involved right now in our arsenic work. So this goes throughout -- this is how we've always operated. We just don't do things within the Division of Biochemical Toxicology. We're very dependent upon the other divisions to accomplish what we want to accomplish.

As will become apparent, we work very closely with the product centers. We address problems that they have, probably to a greater extent than the other divisions do. We are heavily funded by the National Toxicology Program. We've been funded right since the inception of the interagency agreement, more than 25 years ago. We -- and again, it's to address FDA problems, but it's been very helpful for the center financially, but it's also been very helpful scientifically for the FDA.

We get money from the National Cancer Institute,

this comes -- Igor Pogribny has had years of funding from NCI. We don't currently have any funding for the EPA, but we're working on problems that are important to the EPA. Likewise for CDC.

As far as global outreach, a number of us are involved, heavily involved with the International Agency for Research on Cancer. We sit on their monographs program, so we participate in that. We've been involved in the priorities program. We've been involved in rewriting the preamble. I assume that's going to continue. Of course, IARC's part of World Health, but Dan Doerge, for instance, is heavily involved in World Health, and also the European Food Safety Authority, so he's spent quite a bit of time in Parma working with that.

Mary Boudreau is involved with OECD, helping the guidelines for dermal toxicity. And Dan Doerge is involved with the Japanese food safety committee.

This gives you what our mission is and our goals, and really what we emphasize is toxicological assessments. The other divisions tend to be developing methods and so forth, and we will develop new methods as necessary, but I really think the thrust of what we do is we do toxicological assessments and it's based upon we do a lot of bioassays. I'm one of these people who believe that

you're going to be doing animal research. It may diminish, but there's always going to be a necessity for animal research. As part of -- so we do bioassays, but then we also do mechanistic studies so that we understand the response that we obtain in the animal and whether or not this is relevant to humans.

And then in the last 10 years or so, we've added computational modeling. You know, we've always, when John Young was here many years ago, we did modeling but then he retired, but then we've really made an effort to build this group. So you've heard about Jeff Fisher. We have Jeff Fisher, we have Annie Lumen, we have Xiaoxia Yang, who is going to go to CTP, and then we have postdoctoral fellows who worked with him, but we've made a -- and the idea behind there is we take the animal data and try to extrapolate it to humans.

We've asked, what have we done in the last five years, and these -- with the exception of the pyrrolizidine alkaloids, these are all studies that were funded by the National Toxicology Program. So, Bill Slikker this morning mentioned bisphenol A. Bisphenol A was an enormous investment, as Jason Aungst knows very well. It's been a very controversial work.

We've completed the bioassay. We've completed

the reports associated with the bioassay. We're in the process of -- as part of this funding from the NTP, a number of academic investigators were funded, and now what we're trying to do is to somehow integrate the data that they obtained with the data from the bioassay. Hopefully, this will be completed within the next year, but there's no guarantee that that will happen.

Goncalo Gamboa da Costa -- I should mention that those studies were directed primarily by Barry Delclos and Luisa Camacho, and also heavily involved the investigators from CFSAN. Melamine and cyanuric acid was the pet food crisis where pets were fed diets adulterated with melamine and cyanuric acid, and caused kidney failure. It's also a crisis in China where children were fed adulterated formula.

Goncalo Gamboa da Costa led these studies and demonstrated very nicely that by themselves melamine and cyanuric acid are relatively safe. You put the two together, you get beautiful crystals in the kidney, and that wipes out the kidney. These studies, the experimental studies are done and Goncalo is in the process of preparing the final report.

Furan, the impetus behind furan is there was an NTP study that was conducted, and the rats had 100 percent

incidence of cancer, and if you have 100 percent incidence of cancer, even at the lowest doses, it's kind of hard to define a dose response. So we went back and this was restricted to just rats, because they're the most sensitive. Male rats are more sensitive than female rats, and so we did a very nice dose response study. It's a very curious dose response, in that nothing happened until you got to .2 milligrams per kg, and all of a sudden you went to 100 percent. I've never worked with any compound that gave such a bizarre dose response.

These data were requested by CFSAN, but I point out that the data we generated are used by other regulatory agencies. For instance, Health Canada just did a risk assessment based upon our bioassay data with furan.

Bill Slikker mentioned aloe vera. Aloe vera is people -- you think of it as a lotion, but people do drink it. It does cause intestinal cancer in rats. More recently -- this was led by Mary Boudreau. More recently she treated with -- we think the agent responsible is aloin, and she did a short-term study with aloin, and indeed, we get the same types of lesions that were observed with the whole plant. So we think this is the agent that is responsible. We think it should be regulated based upon the aloin content.

Acrylamide/glycidamide was -- I ran those studies. They have been done -- the bioassays have been done for quite some time. The data have been used worldwide by regulatory agencies to set limits. We have continued, though, we want to -- it's very curious, because whereas you get DNA adducts on all the tissue you look at, there's only certain organs that you get cancer, and we're trying to understand that. So we're working -- we're still working doing mechanistic studies with acrylamide and glycidamide, trying to understand the tissue response and is it due to DNA adducts, is it due to epigenetic phenomena, and so forth.

Pyrrolizidine alkaloids, we did not -- we have not done a bioassay with that, but Peter Fu has done mechanistic studies and has demonstrated a common series of DNA adducts that are formed from all pyrrolizidine alkaloids. So the structure of the pyrrolizidine alkaloid differs, but the DNA adducts that you obtain from each one are identical.

Then the last one is triclosan. This was led by Jia-Long Fang, at the request of CDER. Triclosan is used in a lot of detergents, soaps and so forth. It's also in Colgate toothpaste, and CDER needed data regarding the dermal application of the triclosan. So we did that. That

report is in the process of being prepared.

What I'm going to talk to you about, I want to talk to you about four projects that are currently ongoing. Just to give you sort of a flavor of what we do in the division. The first one is arsenic. Arsenic is in drinking water. Everybody is exposed to it. The drinking water limits set by EPA and World Health are 10 parts per billion. If you look at the bottom of the slide, you'll see that the estimated dietary intake to arsenic in the United States, and the key thing here is if you compare adults to children under the age of 1, you'll see that children get much higher levels, anywhere between three- and say six-fold higher than adults. That's very important, because we believe that children, at least if you believe animal data, are far more sensitive than adults to the toxic effects of arsenic.

As far as cancer studies go, if you give inorganic arsenic to an adult rat or mouse, the animal will not get cancer. Mike Waalkes at NIH came along and demonstrated that if you give transplacental-only exposure to mice, you'll get cancer, primarily liver and lung. Then he came along -- and this is what got us very interested -- he came along with what you call a whole-life exposure, where you treat the dams and sires before breeding, and

then through gestation and after gestation, the pups are kept on for the entire life, and what happened is if you look at the lowest dose, the .05, this is 50 parts per billion, there was an increase in cancer in the lungs. Fifty parts per billion is only 10 -- it's only fivefold higher than the EPA drinking water limit.

So that was a great concern. If he was right, what are you going to do with these? The margin of error is not very -- the margin of safety is not very great. There were problems with this study. First of all, the dose response was very bizarre. By bizarre, it was nonmonotonic. I don't like -- I like monotonic responses.

He also didn't get cancer in other -- if you get cancer in the lung, you should also have gotten cancer in the liver and the adrenals and so forth, and he didn't. Now it's possible that as you go to low dose that -- but we felt that there was concern, these data caused us great concern.

So what we did is we -- this is Dan Doerge who is doing this -- is do pharmacokinetic analyses with the intent of could we then, based upon the data that we got from the pharmacokinetic analyses, design the bioassay. So Dan has published four or five papers in the last year, and this is just sort of giving the high points of it, and I

think the important issues, and one is that if you give inorganic arsenic orally, it's readily absorbed. The same thing is arsenic is converted upon ingestion to dimethyl arsenic V. Dimethyl arsenic V is the major -- it drives the pharmacokinetics. It's 99 percent of the AUC.

So that's the second point is metabolism is dominated by the formation of dimethyl arsenic V. A key point here is the kinetics are nonlinear. As you go above 50 micrograms per kg, you tend to saturate metabolism. So what this implies that if you're doing toxicity at doses higher than 50 milligrams per kg, you're going to get erroneous results. You're going to overestimate the potential toxicity.

Another key point is the dimethyl arsenic V is reduced back to dimethyl arsenic III internally. What's key about that is dimethyl arsenic III binds proteins and causes toxicity. So while dimethyl arsenic V has generally been considered to be a detoxification product, that's not necessarily true.

Another key point is that there's very poor lactational transfer of arsenic, inorganic arsenic or the metabolites. So if you're depending on lactational transfer and the critical period of exposure is this perinatal exposure, you're really missing -- unless you

treat the pups directly, you're not getting a true estimate of the potential carcinogenicity.

Based upon that, we put together or are putting together a bioassay. It's going to be composed of two components. One is we need to do the inorganic arsenic and determine whether or not there's this bizarre -- what I would call bizarre -- dose response. Because, as I said, they got lung tumors, but we think they should have also gotten liver tumors, adrenal cortex, and ovarian tumors.

The other point is that there is poor lactational transfer. These are the key data gaps for inorganic arsenic.

For dimethyl arsenic V, there's never been a perinatal exposure. It's always been adults. It causes cancer when you give it to adults. And again, there's poor lactational transfer.

So this is what we're going to do. We're going to treat -- we're going to do a whole life exposure. We're going to treat the dams and the sires before breeding, during breeding, and pregnancy, and by drinking water. Once the pups are born, however, we're not going to depend upon lactational transfer. We're going to dose the pups directly, because we think that's critical. That's what children -- children, if they're eating rice-based food,

they're getting it directly. Then once the pups are weaned, they'll go back on drinking water.

So we're going to do both inorganic arsenic, and we're going to do dimethyl arsenic V. For the inorganic arsenic, we're going to use a very wide dose range. We're only going to use one sex, because we know it causes cancer. What we want to know is the dose response. We don't have to use both sexes.

For dimethyl arsenic V, it's going to be a more conventional bioassay with three doses, simply because we don't know what's going to happen in infant -- when infant mice are treated. This hopefully is going to be funded by the NTP. We've been in discussions. We hopefully have the support of CFSAN, who's responsible for regulating this, and so we will hopefully have this in place and started sometime this fiscal year.

The second thing is PEGylated biopharmaceuticals. This was done -- these studies were started at the request of the Center for Drugs and the Center for Biologics. As indicated here, PEGylation is a process where you put in polyethylene glycol onto a protein. It improves the drug solubility, extends the half-life, increases the stability; it protects it from proteolytic degradation, you can reduce the frequency at which the drug has to be given. These are

all good things.

The problem is there's been several PEGylated biopharmaceuticals have been associated with PEG accumulation and cellular vacuolization in various tissues, including the choroid plexus, and this caused concern to both biologics and Center for Drugs. The other problem is that the use of these drugs have changed, and now it's being used in pediatric medicine and it's being used chronically, which wasn't done previously. So the issues are what are the tissue -- is there tissue accumulation with time? What are the long-term effects if there is accumulation?

We intended -- this study is being directed by Jia-Long Fang, and we had intended to start with the second bullet, followed by the third bullet, and then the first bullet. To do the toxicokinetic profile, we needed radiolabeled material, and we have so far been defeated in making radiolabeled material. We obtained very pure material. We rigorously characterized it. We attempted to do tritium exchange, and that just blew the molecule to pieces.

So we still have ideas of maybe putting some carbon-14 extensions on the end of the PEGs, but for the time being so that we could at least get this study going,

we have started with the first bullet, where we are doing a toxicological assessment in animals treated subcutaneously, intravenously, for 24 weeks, and we're using three different molecular weights to see if the molecular weight, how the toxicity changes as a function of molecular weight. This study is, I guess we're about halfway through on the treating.

Another study that we're doing is -- Bill briefly mentioned this -- is nattokinase and lumbrokinase. This was done in collaboration with investigators at CFSAN. These are serine proteases that are taken -- they're dietary supplements. They're promoted to -- because they help cardiovascular and circulation health. One comes from Bacillus subtilis. The other comes from earthworms. People apparently take this.

Anyway, Luísa Camacho is the person who is running this study, and if you have questions, you can -- but the concern is there has been at least one case report where a woman was taking -- I forget either it was nattokinase or lumbrokinase and aspirin, and ended up with cerebral hemorrhage, and the question is if these two are taken together, does it exacerbate the effect of aspirin. So to address that, the lumbrokinase and nattokinase is being administered individually or in combination with

aspirin, and the doses are here. It's a 28-day study in Sprague-Dawley rats.

This shows all the endpoints that are being measured. The animal work is being completed. The measurements are currently being made, and with one exception that I'll show you on the next slide, really not very much is going on.

The one thing that Luísa has been able to observe is shown on the left side. So we have lumbrokinase on the left, nattokinase on the right, and what I'd like you to focus on is just the green bar, the third bar over, that has the asterisk. That's just aspirin by itself. Then if you give lumbrokinase with aspirin, it masks the platelet, the inhibition of the platelet aggregation caused by aspirin.

It's not something we expected. We don't really know the reason for it. Luisa suspects that lumbrokinase may have some esterase activity and cause the decomposition of the aspirin, but at the moment we don't know this, but as you can see, it only occurs with lumbrokinase and not with nattokinase.

So this, again, is a direct -- this is a problem that CFSAN asked us to address, and I should point out in all of these studies, we don't just set up a study by

ourselves and say here are the data. There's a tremendous back and forth interaction between the product centers, because we want to make sure that when the study is completed, it's data that they can use. So we go through this iterative process to design a study that meets their needs.

The last one, and this was conducted in collaboration with investigators from the Center for Drugs, was funded by medical countermeasures, and it deals with oseltamivir, or Tamiflu. This study -- well, Goncalo Gamboa da Costa has done the experimental portion of this, and then Annie Lumen is doing the modeling. This is what happens when you give oseltamivir to pregnant women?

Pregnant women seem to have higher mortality and morbidity and mortality from influenza, and this morbidity and mortality increases as the pregnancy progresses. Oseltamivir/Tamiflu is known to -- it is an effective drug for treating influenza or for prophylaxis. The question -- and when it's given to pregnant women, it seems to help. But the question is what is the proper dose to give to a pregnant woman?

So the objective of the study was twofold. One is to determine whether or not rhesus monkeys were a good model for pregnant women with this. So that's sort of a

bigger role. The second was to determine the pharmacokinetics. Does the pharmacokinetics of oseltamivir, both the parent drug and its active metabolite, which is the carboxylate, change as a function of pregnancy?

These are a lot of experimental data just compressed to show you that as a function and a paper describing this is in the final stages of preparation, and it just shows you that as a function of trimester, so we have nonpregnant animals, first trimester, second trimester, third trimester. Really not a great deal is going on. There's not a great deal going on, but there's not a lot of change as a function of gestation. These data and literature data are now being used by Annie Lumen to do pharmacokinetic modeling and extrapolation to humans.

And ending -- okay, remember we were supposed to have this meeting in December, right? It's been a long time. Anyway, then we had the shutdown, which was the worst shutdown I've ever been through.

Anyway, what I'd like to point out is we haven't stopped doing things during the -- since December. These slides were put together in December. What I would like to point out is things we have able to receive additional funding. Mary Boudreau has recently -- Bill Slikker talked

about this perinatal center, perinatal health center of excellence. PCHE. In collaboration with investigators at CFSAN, she has received funding to determine the disposition of tattoo inks in pregnant mice. As everyone's aware, tattooing is rampant in the United States now. We have no idea, does it -- most people think that nothing happens, but about 90 percent of the dye disappears. The color is still very intense, but where does this go?

Especially, is it being transported to the fetus? So she has just received funding to do that, in collaboration with investigators at the Center for Drugs, we just recently received funding to study cannabis, and the issue there is are people who are -- it's being used medically now. Are they exposed to heavy metals? Are they exposed to bacteria? And so we will be looking at that over the next year.

Annie Lumen who does the modeling has received funding from the Office of Women's Health for one project, and also from the perinatal center for a second project. Igor Pogribny has received funds from the Office of Minority Health. Then Dan Doerge who has done -- who does a lot of the pharmaco -- the mass spectrometry-based pharmacokinetic analyses, has a collaboration study with people at CFSAN that is going to look at perfluorinated

compounds and how these are metabolized and so forth.

So financially we are doing okay. We don't still have a budget, but other than that, things are cool. Our biggest issue as far as I'm concerned as a director of a division is the ability to recruit people and bring them in, you know postdoctoral fellows and so forth, is absolutely essential for conducting science.

With that, I'm done.

(Applause.)

DR. LEIN: Thank you, Fred. Questions, comments, from the SAB?

Susan?

DR. FELTER: Susan Felter, SAB. Thanks for the presentation. My question is to what extent you have the capability in your repeat dose studies, so the arsenic study being an example, to incorporate some of the newer technologies, something like toxicogenomics, evaluations of, or transcriptomics of target organs, to see if we can start to build our understanding better of genetic level changes as they correlate to apical changes associated with histopath, for example.

DR. BELAND: Okay, that is being addressed to some extent by Igor Pogribny. He's at the present time is doing it a cell culture based approach, and I'm not sure we've

looked at -- he's looked at animals, and I know as far as changes in the microbiome, Carl Cerniglia's people in Carl Cerniglia's division, they're looking at that as a function of dose with arsenic administration. So we have the capabilities. It's being done to some extent.

DR. FELTER: It might be something we're seeing more advances being made in this area, and as we try to focus more on human relevant doses where the question is always do we have a large enough sample size to see whether there's really something happening, rather than focusing on higher doses to try to generate a response that then we have to follow up and understand the mode of action when it might not be relevant, can we focus more on lower doses and increase the data generated at those lower doses?

DR. BELAND: The doses we will be using for the arsenic study are only fivefold higher. We're going to go down to 50 parts per billion. This is not a high dose study at all. You're absolutely right there. It's critical that we get to human relevant doses. One of the issues we're facing with the arsenic is -- and was not addressed in the Mike Waalkes studies is -- the diet, normal rodent chow has a lot of arsenic. We've spent a lot of time finding a diet that can be administered in a two-year study. But the diet is going to contribute about 50

percent of what we administer.

DR. STICE: Steve Stice, SAB. Nice presentation, Fred, thanks for all the work you're doing. I was interested in how your data or modeling or animal studies fit into AOPs and what the adverse outcome pathways that the EPA and NIH are extensively working on, and then the second question is are you thinking about other I guess factors such as co-exposures to other toxicants like alcohol or cadmium or some of those issues, as well.

DR. BELAND: Mixtures are a problem. I have tried to get the NTP to pay for some mixture study and was never successful. So as far as doing combinations, other than what Goncalo, we mentioned the melamine and cyanuric acid, that was by themselves and as a mixture. So typically we don't do that.

As far as the adverse outcome pathways, I don't -- Annie Lumen is involved with the Tox21 consortium, and I don't do modeling. So I really can't address it beyond that.

DR. STICE: The information you're generating, I'm sure when published will be added to that, that adverse outcome pathway analysis, but some of those things might be useful to think about in more extensive discussions with EPA and others.

DR. BELAND: I know the papers that Annie Lumen has published, is being used very extensively by the EPA.

DR. LEIN: Pam Lein, SAB. So great presentation, Fred. Something occurs to me, because we also have recently gotten involved in these long-term exposures. A two-year exposure is heroic, and given the value of the tissues to be generated from those animals, in the context of Susan's question of how many endpoints can you internally afford to look at, is there any sort of mechanism for making tissues you're not using available to investigators, either in other centers or outside of the FDA?

DR. BELAND: Okay, for these studies, they're typically -- you know, traditional histopath. So we have formalin-fixed tissue, and we use that to do other studies to the extent that it's possible formalin-fixed tissues. The bisphenol-A studies, there were extra animals that were used by academic investigators. If something is built in at the beginning to collect fresh-frozen tissue or something like that, that can be done. But it has to be built in at the beginning of the protocol rather than in -- they're typically additional animals, because the bioassay animals is done GLP and there's a prescribed format for how that tissue is handled.

DR. LEIN: But maybe just an approach to think about, as NCTR moves forward in the future with more demands and less resources, is designing those studies to make tissues available. Maybe you don't need the full brain. You can use half a brain and save half a brain for somebody else. But just a thought, to leverage some resources you have.

Do we have any questions or comments from the centers?

Oh, sorry. Steve?

DR. STICE: One more question. You described studies in rodents and monkeys as well. How do you go about deciding which model or which species to work in when you set out to do studies? Just curious.

DR. BELAND: Okay. As I pointed out with furan, we had bioassay data before, and so we restricted that to a male Sprague-Dawley rat, or Fisher rat, I'm sorry. As far as if we don't know anything about the chemical, we typically do both mice and rats, both males and females, because you can't restrict a single sex. As far as then a step up from the rodents, traditionally we've used rhesus monkeys. We have a huge rhesus monkey colony here, but typically these treatments have been done off site simply because of the constraints on the animals that we have

here. They're being used for other studies.

So I can't -- it just seemed the next logical step to go from rodents to monkeys and then, if possible, obtain human data.

DR. ASCHNER: Michael Aschner, SAB. Thanks for the presentation. Just a follow-up on what Susan said, what you might want to consider is crosstalk with the Division of Genetic and Molecular Toxicology. I think they can be quite helpful in addressing genetic susceptibility to arsenic and those kinds of types of studies.

DR. BELAND: We're not doing a specific like that, but there's this collection of mice called the collaborative cross, and it supposedly covers the whole genetic diversity of what you would find in humans. Igor Pogribny is conducting studies where these various strains of mice are being exposed to various agents. My personal take on it is the exposure is far more important than genetic diversity, as far as the response that's being observed, but that's my personal bias. You don't have to agree. I told you it's my personal bias.

DR. FELTER: Susan Felter. So maybe just to follow up on that theme a little bit further would be to look at things that tie into the AOPs that Steve was talking about. So for example, if you looked in target

tissues and look at liver and lung in animals and you might not even need -- you can even take animals that have only been dosed for a week or two weeks, and see if there are pathways that are upregulated or DNA repair pathways upregulated that might indicate a concern for primary effect on DNA. Is there a level, an exposure at which you see no upregulation of genes that would indicate maybe a biological threshold? So that's really at the heart of it.

DR. BELAND: We have a paper that just came out, I guess it's out, it's the newest issue of Chem Research in Toxicology. It gets back to the target organ specificity for acrylamide, and we looked at DNA damage. It was identical in the liver, which is not a target issue, which really surprised me when we did the bioassay, as opposed to the lung which is. We have looked at epigenetic changes and changes in gene expression, and as a function of dose, and there are differences, and you can make arguments to why the liver is resistant and the lung is -- so we are using such an approach. We are not ignoring that altogether.

DR. LEIN: Any other questions or comments from the SAB?

Okay, now it's your turn. Any questions or comments from the centers?

DR. RUIZ: Juan Ruiz, CDER. In the PEG tox studies that you presented, and thank you very much for a great, informative presentation, are those neat PEGs or actually PEGylated proteins or other --

DR. BELAND: No, they're neat PEGs. We've discussed that. What we wanted to do was to start with -- because there's a whole variety of proteins that have been modified by PEGs, and so we thought we'd start with a pure PEG and look at it as a function of molecular weight, and then depending upon what we see, then the next step would, in consultation with both drugs and biologics, is where we would go from there. So our approach has been we don't try to do everything in one pass. Let's do experiment, find out what we get, and then make a decision as to where to go from there.

DR. RUIZ: Thank you.

DR. LEIN: Any other questions or comments?

Okay, my last comment or question, I guess it's both, I was really excited to hear you are looking at cannabis in the prenatal health center, because there's a lot of -- if you go online now for forums for pregnant women, they're all advocating the use of cannabis for controlling pregnant-related nausea. So this is becoming a huge issue. But I was a little surprised at the focus of

the study. So is there any intent to look at cannabidiol versus THC in the context of the developing brain?

DR. BELAND: First of all, the cannabis study is not for perinatal.

DR. LEIN: Oh, sorry. Did I get that confused?

DR. BELAND: Or maybe I misspoke, but no, that's directly out of Center for Drugs, and it's Center for Drugs funded, and their issue is that they're receiving new drug applications and they're concerned about what these people are being exposed to, not pregnant women, just people. They need to be in a position to address, and they're concerned that our involvement is whether or not the vapor contains heavy metals and whether the vapor contains various microbiological contamination. This does not involve animals at all. It's straight analytical chemistry. And then we're using, we have smoking machines and we have vaporizers or what are they called? Volcanoes.

DR. LEIN: Yeah, that's a huge issue, too. In fact, I go to Philadelphia in two days to give three talks on vaping to middle school and high school. So this is a huge issue right now.

My question is in your purview or in the NCTR's purview in the near future, is there any intent to look at the developmental neurotoxicity of cannabidiol?

DR. BELAND: Bill, this is your history.

(Laughter.)

DR. SLIKKER: Well, it's an open question, because there is a lot of interest within the FDA as to how this entire class of compound will be handled. I will say that we have a long history in working with marijuana smoke and delta-9 THC, the active ingredient, and have done the placental transfer studies in a variety of animal models, and also looked for chronic exposure to marijuana smoke in rhesus monkey populations, with a year and a half of exposure, complete analysis of behavioral endpoints and then at the terminus, neurochemistry, neuropathology, et cetera.

So there's a lot of information that we published in a series of 15 papers over 20 years ago. That doesn't meant that there isn't more room for opportunities in the future to understand some of the effects on the developing infant and/or children, and also some of the more pertinent questions today that have to do with perhaps the vaping or other exposure routes in addition to the traditional smoking paradigm.

Or even oral, which is commonly available in most of these, some 30-plus states that provide recreational and/or medical use of marijuana products. The oral

consumption, as you know, is a big portion of that nowadays. So I think there's room for additional work here, and we are definitely in a position to address that, because of our long history of working in this field.

DR. BELAND: I have one question. By vaping, you mean the nicotine delivery devices, correct? Or are you talking about cannabis?

DR. LEIN: So yes, they're vaping cannabis, and they're also consuming cannabis in oral preparations. But it's becoming a really big deal for pregnant women to control nausea, and with the research coming out on the role of the CB1 receptor and the development of the brain, I think that's a huge data gap, and one of my recommendations as an SAB member would be that this would be an area to consider, because I think there's a dearth of information on it.

DR. BELAND: But the study we're doing is directly at the request of the Center for Drugs, and they're very clear it's a very focused study.

DR. LEIN: Got it.

Okay, are there any other questions or comments around the table?

Okay, thank you very much, Fred.

Oh, sorry.

DR. AUNGST: Jason Aungst at CFSAN. I just wanted to say it's nice work here. I think CFSAN has had really good and productive collaborations over the years with the NCTR. We have had a lot of good studies done there really testing things that you probably couldn't get tested anywhere else. That's been really positive, and you brought up the cannabis, and that's something we're not touching yet, but yeah. Some places it's edible. Not federal yet.

DR. BELAND: We have a new production facility that opened I think this week right next to NCTR, because we now have medical marijuana that's been approved in Arkansas.

DR. AUNGST: So it's coming.

(Laughter.)

A couple of things. I just wanted to -- a reminder that things you talked about like tattoo inks, that also falls under Center for Food Safety and Applied Nutrition things you might not think about there, as well as a grant for the perfluorinated compounds, and I think both of those we're looking at pharmacokinetic modeling, which is a newer area, and even within CFSAN we have recently hired pharmacokinetic modelers to help do this, and they work very closely with Jeff Fisher, Annie Lumen,

and others at NCTR to work out the focus towards the regulatory data gaps and build those models to get what we need for use.

Thanks, Fred.

DR. LEIN: I will look at each one of you now when I say this: are there any other questions or comments around the table?

Okay, thank you, Fred.

(Applause.)

Agenda Item: Division of Bioinformatics and Biostatistics, Weida Tong

DR. LEIN: So next, we have a presentation from Weida Tong, Division of Bioinformatics and Biostatistics.

DR. TONG: Well, thank you. So what I'm going to do is just tell you on every moving parts in our division and when I say every moving parts, after I finish my presentation, you will know a lot of the moving parts in the Division of Bioinformatics and Biostatistics, and we have a little bit over 50 people. They are very much evenly distributed across four branches. Bioinformatics branch, biostatistics branch, R2R branch, that's the new branch just established in a couple of years ago, and the scientific computing branch.

I'd like to draw your attention to the vacancy we

have across all the branches, and we are being operating at more like than 20 percent of the loss of its normal size, for several years now. So this is going to be one of the questions by the end of my presentation to you, how you can help us or make a suggestion to recruit young talent people come to NCTR to work. I think we are facing very much the same issues as Fred already mentioned in his presentation.

So if I can describe what this division is, I can use only one word, multidisciplinary. You are very much be able to find all the expertise in the IT area and in this division. We have a scientist doing the bioinformatics and biostatistics of course, and computational and toxicology, chemoinformatics, and even biology. So at this point, and we have a 40 percent activity was devoted on research and about 60 percent is on the support.

So what I'm going to do, I'm starting with the support, starting with talk about what kind of support within the NCTR. We are handling a lot of the legacy activity, and legacy activity means this activity already existed before the division was established. For example, the scientific computing branch and the closely work with OMIT to serve as more like a computer center to support the entire NCTR. In our biostatistics branch, we also have statisticians designated to support the NTP and CTP

program.

The things the division was established and backing to 2012, so we also established a bioinformatics support program, and the way we do things here is first we have several in-house software, like ArrayTrack, and ArrayTrack was developed some years ago now for the microarray data management and data analysis, as well as data interpretation. At one point, it was used for supporting the voluntary(?) genomics data submission program at FDA, and it's still being used by some scientists from other centers, as well as at NCTR.

Now there's everyone talking about a next generation sequencing, you're going to hear more about next generation sequencing project at NCTR. So in order to support these activities, we set up a Galaxy platform and to implement various bioinformatics pipelines so the other division will be able, particularly these scientists not trained to do the program algorithm, and they will be able to get into the Galaxy platform we set up and pick and choose the pipeline to analyze the next generation sequencing data.

And we also set up a high-performance computing environment to support big data analytics across the divisions. Of course, we provide the trainings and to make

sure the scientists not only just aware of these capabilities available to them, but also how to use them.

And in terms of the collaboration with other divisions, and I'm not going to go through all of these projects in detail, basically we routinely being call up as a co-PI to work on various projects in the various divisions, and in most of them, actually, related to the genomics or the omics data analysis. Nowadays, a lot of the works are related to the next generation sequencing data analysis.

So now I'm going to talk a little bit about collaboration beyond NCTR and how we interact with other centers. This slide is not intended to be a laundry list, and highlight some of the projects we are working with CDER. Actually we have more than the one we list here.

Dr. Slikker already mentioned about DASH. DASH is the tools used to provide information about NDA and BLAs, and as well as the information how the IND was progressed to the NDA and the BLA approval process. So the DASH program has been widely used in CDER, not only in the review process, but also by the upper management team to provide information to respond to congressional inquiry. So we did not develop these tools. I just wanted to make sure it's Office of the Translational Science that

initially developed these tools using the access database, and then these tools become very popular. Everybody hit the tool at the same times, as nothing works.

So we have been called in to upgrade these tools into the Oracle environment, and then we build the front-end to allow the information easily flow into the database, as well as provide the data visualization capability.

So because the success of the DASH program, next thing we are being aware was being called in to dealing with so-called breakthrough therapy designation. Now breakthrough therapy are those drugs are used to treat serious conditions, has been proved very effective compared to the in existing drugs on the market. So once the breakthrough therapy has been identified by FDA, FDA can provide expedited review. It's a very big deal to the pharmaceutical company, and of course, we have been asked to develop independent tools to bring these information into the DASH environment.

We also very closely work with the Office of Computational Science. This is one of the office under the Office of the Translational Science, and we have a number of projects. I listed these three, because these three really present the breadth and the depth of the work we do with this group. The first one is called IND Smart

Template. Now, when pharmtox reviewer to receive the IND, there is a certain template in the Word document, they start to type in the information, during the review process, and then this paperwork is stuck away in the box, and if the new reviewer coming in cannot even find it, it's very difficult. So what do we do? We first don't want to change anything they are doing.

All we did is build a backend database. Every time somebody types in, the database would suck the information into the database, and then starting to provide the suggestions. Hey, like Amazon, like the tools, someone looked at this very similar review already been done, you might need to look at that kind of information.

So IND Smart Template has been very successful and more recently we have been approached by OND, Office of the New Drug, they want a very similar function available to the OND, the NDA and drug review, and of course, the text-mining become very important. Once the information was captured in the database, we need to have a way to compare these texts.

So text-mining is sort of the core competence in this division, and we do a lot of text-mining here. So we help the OCS to extract the information and doing a lot of text-mining, and the next thing we know, and we have been

approached by OND because OND conduct a lot of the meetings with the sponsors, and every time the meeting was finished, there is a meeting minutes. It's a lot of information is meeting minutes and then they summarize it, and it becomes a piece of paper and is stuck away.

So what we did, we used the text-mining, pulled out all this information, put in the database. This becomes extremely useful. Think about it. The turnover, we were talking about the turnover all the time in Arkansas, more than in D.C., but actually more safe than D.C. But the issues is how we can maintain corporate or institutional memory, and this is really what we do. If we will be able to capture all of this information in the database, and the new person coming in can be easily to find this information. This is what we do.

Another project very much considered is start project not from my group, actually let me just explain a little bit about this project for the FDA label. Now everybody knows about the drug labeling document. If you get a medicine from Walgreen, you will have a small piece of paper. You will not be able to read it. This is a simple version, simplified version, of the large FDA drug labeling document, normally about 20 pages, 80 sections, each section provide the very different information. For

example, the information how to take the drugs, what's the efficacy, and what is the drug/drug interaction, and what kind of adverse events you should be aware of. So those information made available to the doctors and patients and they take, they look at this information, and they can substitute the drugs or take the drugs more appropriately.

Right now we have a little over 100,000 FDA labeling documents, and this information has been routinely used in FDA in the review process. How you can access that many information by the reviewers? So what we did, we developed a database and provide all the bells and whistles the reviewer needed to find the information, and we are not only just provide the bells and whistles, and these bells and whistles are designed by the reviewer and from the FDA labeling team, they pointed out what kind of functions they really needed in these tools to support the review process.

Now I need to point out we are not lead of this process. Actually Dr. Hong Fang from Office of Scientific Coordination at the NCTR lead this project, and my division provided the technical arms and Dr. Qiang Shi assisted somewhere from the Division of Systems Biology, he provided expertise to implement in his project I mentioned about in FDA and the labeling team, and however, Office of Computational Science in CDER really did a heavy lift.

They went out, talked to the users, and provided trainings, and make sure the user really aware these wonderful tools are available.

Last year, I gave a presentation and talk about, in here, SAB, I talked about these tools, and Dr. Robert Bosman(?) actually from the OGD and he found it is wonderful. Now the Office of Generic Drug in CDER, and we are starting to work with them to implement the specific functionality to support OGD and review.

Now, when I talk about FDA label, I DoD need to mention about the risk evaluation and mitigation strategy, called REMS. I don't know who came up with this name. It's very good. REMS capture the serious, severe adverse events happen to certain medicines, and it's a drug safety program, and using the exact same structure as drug labeling document. So we have been called in to sort of develop very much the same thing and particularly how to disseminate these REMS information through the website and to the patients.

So this is the work we are doing with the CDER and of course I do want to point out and CDER is not only the centers we are working with. Of course, in most of the projects we have from CDER, and we also very closely work with the Office of Regulatory Affairs, particularly we take

advantage of the Regional Arkansas Regional Laboratory in here, and for example, one of the projects we are working on right now is develop a LIMS system to track every step of the review process, the information associated every step of the review process into the LIMS system as a prototype.

This project was requested by information system management from ORA, and we have another project called the International Mail Facility, and there's a lot of the packages was shipped into the United States and landed in the International Mail Facility. So ORA needs to look at this package, particularly these packages associated with drugs, and this is a very labor-intensive process. So what do we do? We develop AI, artificial intelligence, based systems to help reviewer to quickly identify which packages need to surface on the top to be evaluated first.

I'm going to talk a little bit more later on about what particular AI-based systems we are developing in our division, and we used to have several projects with CTP. The one we just completed in the last year is using the computational toxicology methodology to assess addiction.

Okay, so now, I talk about some of the support functionality in the division, and within the NCTR, and

beyond NCTR. Now I'm going to move to some of the research project that we are doing in our division. What I'm going to do, and just like other division director will do as instructed, I'm going to talk about the top three accomplishments in the past five years. I'm going to talk about one from the precision medicine area, one from the rare disease, and one from the drug safety.

Then I'm going to talk about what kind of projects are going on at my division, and of course, we are very active in all these areas. What I'm going to do, I'm going to talk about how we are evaluating the toxicogenomic system and why this is important.

Then lastly, I'm going to talk about the future direction, and specifically I'm going to mention about artificial intelligence. Now it's like everywhere, but for me, you cannot even take three steps into the field of the bioinformatics and biostatistics without stumbling on the AI. We have been doing that for a long time.

What I want to do in this presentation, I'm going to point it out, what specific AI algorithm we use to support the regulatory missions, not talk about the research. Okay? First accomplishment, and Dr. Slikker already briefly mentioned about one of the large consortium activities we are leading called the Microarray Quality

Control or the MAQC. As the name suggests, this project has a long history people study with the microarray, and actually we study in 2005, and now by 2014, we just finished the third project of the MAQC. We have all those paper was published. Throughout all the projects we do, in this consortium effort, we always ask a very simple question. If you have at the same samples give to the different labs, they can sequence or profiling differently, using different machine, and analyze differently, are they going to get the same biological interpretation?

So this is a simple question. On here it's basically an illustration. This is a phase III project we do, and we have six reference samples we give to the 11 labs. Some labs have only Illumina machine. Some have all three. And we really don't care. We just give them samples. They give us data. Now we be able to conduct a cross-lab reproducibility in the cross-platform reproducibility. That simple concept actually lead to the massive operation, generate a huge amount of data, by the 2014, when we finished this project, we generated over 10 terabyte data, for next generation sequencing RNA seq in this specific cases. When we deposit into the GEO, our data represents 6 percent of all the RNA seq data in the GEO. Now we are very proud about this, because we feel we

contributed to the research community, and about the data. So people may be able to use it.

Accomplishment number two is about the Liver Toxicity Knowledge Base, and this is the project that was dealing with the drug-induced liver injury. Now I'm not going to talk about why that is so important of the drug-induced liver injury for this audience. You're already aware. I do want to point out one specific effect, and this is also the motivation behind this project. Over 40 percent of the drugs was failed in the clinical trial due to the liver injury. It's never detected in the preclinical space. That means whatever the model we use in the preclinical space, it just not very effective to determine which drug is safe, which is not, when move to the human, okay?

So because of that, there is a lot of the new technology was introduced in this area, including the genomics and in vitro assay, in silico, so on and so forth. So what we do in this project is collect all of this information, all of this data, put into the database, and on top of that, we develop predictive models. So concept is very simple, and we have done that for about eight years now, and some of the models already been adopted by the FDA in the review process, as a consortium. It's not part of

the review process. I just want to be clarified. We have been consulted over 20 cases somewhere. Here. These cases range from the IND, NDA, as well as the post-market and process. We also made several publications and joint publication with the CDER scientists.

Dr. LEIN: You have nine minutes left.

DR. TONG: Nine minutes left, okay.

So very quick. Just want to point out, Nature Medicine, a couple of years ago writing the article about these programs and explain it, you know, what this program, how it is going to impact into the research environment.

The third accomplishment is about rare disease, and we have a little bit over 7,000 rare disease has been identified, and together impact about 30 million patients in the United States alone. However, the therapeutic option is very much limited.

So what do we do? We believe on the always have some sort of drugs already on the market will be useful for certain rare diseases. So we use the computational way to quickly screen systematically evaluating the market drug and see how these drugs will be used to treat what kind of the rare disease.

So talk a little about the toxicogenomics and how we conduct the evaluating the various toxicogenomic

systems, and this is the paper we just published in the Trends in the Pharmacological Science, and of course the toxicogenomics, a 2020 vision, and within them, we talk about how we are going to deal with the toxicogenomics. What do we see in the future of the toxicogenomics?

One of the things we pointed out is about a testing system. Now, this part is familiar to everyone. This is called a toxicology parallelogram, and we develop a model from the in vivo, in vitro, and from both rat or humans, try to assess the risk in the humans.

So in each domain, we also know that there are many different assays available, each assay was developed for very specific purpose, but we asked the question if we are going to look at the gene activity from this assay system, do they do the same thing or do the different thing? Okay? This is the question we asked.

For example, if the one-day experiment give you the exact same information, so 28 days, why we want to do the 28 days, right? If the in vitro give you the exactly same information in vivo, why we needed to do the in vivo? Now we have a fancy name for the in vitro in vivo extrapolation, called IVIVE, and basically a lot of people were thinking about this and questions, and again, I want to point out one more question. In the biological field,

particularly in the human in vitro, we use a lot of immortal cell line, particularly cancer cell line. Is that a cancer cell line contained gene activity predict the liver injury? Well, they are not even in the same organs, and some paper already published they do.

So this is what we do. I'm not going to talk about common approaches. Usually we do is we have single drugs, look at the different systems, see how many genes are overlap, and then we look at the pathways of the overlap the genes whether they're consistent with our common understanding. If they are, great. If it's not, and we think that these two systems we're dealing with different information.

What we do is we treat each testing system as a magnify, and we ask a question what kind of the resolution of this magnify is going to separate these two drugs? Then to the extent to rank order all these pair of the drugs correctly, so this is the question we ask, if they gave the exact same ranking order, we consider these two systems are the same. So this is just the cartoon ways to illustrate how that works. You have A, B, C, three drugs, with testing the three different testing systems, and we can rank order different pairs. If these two pair at these rank order of the different drug pair, it's the same, we

consider these testing systems same.

I'm not going to explain what kind of the dataset we use. It's a very large dataset, over 20,000 microarray experiments were done in this dataset we used, to assess or to test whether this methodology works.

This methodology we use called the pair-ranking method, called PRank, not called prank. Just wanted to be sure. Called PRank, and we look at whether one-day single-dose study are similar to the 28 days repeated dose study. Actually they are. Scores extremely high. We found in vitro to in vivo is also very high, and we even found that both in vitro assays are very similar between using the human primary hepatocyte or using the rat primary hepatocyte.

The reason I want to mention this methodology. Because this methodology is not dependent on the testing systems you use, I can apply this methodology using the in silico data or the in vitro data, whatever the testing system you use. We will be able to do the head-to-head comparison of using this methodology.

Future directions. As I said, there's a lot of things we want to do, and this is the list of the things. I feel it's important and how to guide this division in the next five years, and the first of course artificial

intelligence. We want to develop a so-called DeepSAFE. SAFE stands for screening, assessment, of the food entry, and from the overseas to the United States. We try to use the deep learning to do this part of work. We also develop DeepLabel. That's took the 100,000 drug labeling documents, applied the deep learning, tried to pull out the information to support the review process.

We are also going to do the DeepFAERS and FAERS is a very large database, and you can do a lot of things with our tools.

Probably I'll just stop here.

(Applause.)

DR. LEIN: All right, thank you.

Questions from the SAB, or comments?

Questions or comments from the centers?

DR. WILSON: Carolyn Wilson, biologics. Could you explain what DeepFAERS is? You probably know there's a lot of work going on in the centers around adverse event reporting systems and applying AI, and I'm just wondering, are you aware of that and working collaboratively and not duplicating?

DR. TONG: Absolutely, yes. I know it's have a lot of discussions and using machine learning method, you know, the FAERS has been looked at, examined by many, many

different methodologies, and when the deep learning is coming, everybody getting very excited, seems to everyone deep learning might be able to take advantage of the information and in the FAERS database, and I also aware there is -- actually there is one project was funded by chief scientist challenge grant using the FAERS database as well.

So what we are trying to do using a different methodology and particularly emphasizing one specific aspect of the deep learning, deep learning actually is very broad. There's different methodologies available, and we have not reached out to talk to the various scientists in FDA yet. This is certainly something we are going to do.

DR. LEIN: So Weida, I actually do have a question. I see up here your second bullet is to evaluate data from animal-free methodologies for regulatory application. There's a lot of effort going on in that same arena in Europe. Are you guys engaged with the Europe EU scientists working on this?

DR. TONG: Absolutely, great question. Now I can talk about this bullet point. So what we tried to do, you know, we know a lot of the drugs have been looked at using various different methodologies, and some using the genomics technology, some using in vitro. So what we did

is we collect all of this information, and we use the same set of the drugs that have the data from the in silico approach, have the in vitro approach, have the genomics approach. Then we do the head-to-head comparison.

A lot of the study, if you look at the comparison in the literature, most of the study was saying I looked at this set of the drugs, and we found that this assay is better. Then another paper says I looked at another set of the drugs, and this method is better.

On the head-to-head comparison, for us it's really important, you really need to look at the exact same set of the drugs, but have the variety of the new data stream, and do head-to-head comparison. So this is the project we are doing. We communicated with the HESI, and Mark is back in there, he knows we talk to the HESI many times, and now we have talked to the Tox21 and we're trying to -- Donna received my request, had to incorporate into the Tox21 program for this project.

DR. LEIN: So we do actually still have 15 minutes for comment. So if you would like to advance to your last slide, you might get some feedback from the SAB on your questions.

DR. TONG: Thank you. So as I mentioned at the very beginning of my presentation, very, very difficult to

recruit the young talent people and into our lab, and we have quite a bit of turnover. We're still running at like a 22 percent loss of normal capacity. So I really need to get some feedback, and also if you can spread the word, that's even better.

Also, there is a lot of data that's available. Nowadays it's not about the generated data. It's find the data very useful. There's several journals, for example on the scientific data, that's the only thing they do is publish the data without any hypothesis. If you put a hypothesis in, the paper going to reject it. They want to have different eye to look exactly the same dataset, what kind of hypothesis that can generate, this particular journal was by the Nature publishing group. So there are several, this type of journals, and we have a journal club by looking into every dataset ever published in these sort of journals and see whether they can be useful.

We are specifically emphasize look at the real-world data, how to translate the real-world evidence, and to support FDA regulatory process. If you have any suggestion in this area, that will be great.

The last one is the technology always evolving and advancing, and if we might miss some of the new technology and you needed to make me aware, and if you have

any suggestions, I would really appreciate it.

DR. LEIN: Okay, thank you. Any comments from SAB?

DR. STICE: Steve Stice, SAB. On your last bullet point, we're involved in a large NSF center grant for cell manufacturing, and I think that's an area close to my heart on things that are -- you know, we're going to be generating large amount of NMR data, mass spec data, cell assay data, of all kinds of things, and bringing that all together and marrying that with some of the clinical outcomes. So for CAR T cell therapy, there's a -- why are there non-responders in an autologous cell therapy type of thing, and can you do that by understanding some of the properties of the cells and what they're doing?

So there's a lot of data that's being generated, and bringing all those datasets together and then predicting what you could do during the manufacturing process to make it better, or just to advance the knowledge as to how to advance the manufacturing process, and I know that's other areas in FDA as very interested in those various centers, as well.

DR. TONG: Thank you, and we definitely -- I will talk to you a little bit more about how to utilize this data, and we, in our lab, at one point we dealing a lot of

the high content screening assay data. It's sort of the imaging data, like what you just mentioned.

We have a little bit of experience in that area, and that would be very interesting. Thank you.

DR. LEIN: Pam Lein, SAB. Along those same lines, you mentioned high content imaging, which of course I think is going to explode even more than it already is, but there's also microelectrode arrays, which are being used not only now for neurons, but also for cardiomyocytes and doing a lot of drug screening, and I know we struggle with trying to analyze the amount of data that is generated by an MEA, and I think that's just going to grow. So maybe another area to think about. With respect to your first bullet, what do you think are the issues you're facing in terms of recruiting and filling your vacancies?

DR. TONG: So, this is very competitive market, and I'm not going to talk about we are competing with the east and west coast. Of course this is very different atmosphere down there. Even just competing locally, and I found it's very difficult and, for example, now some months ago now, and they're closing one of the biostatistics groups in the local university, and there is like eight or nine people let go, and we would not be able to hire any one of them, and the next thing we know, they already have

three job offers and blah-blah, and the salary they pay is higher than what we have in NCTR. So it is very difficult. It is a competitive market, and all we can sell is the enthusiasm and do the good for the public health, and that's pretty much it.

DR. LEIN: I have no words of wisdom. We face the same issues in academia.

Okay, do we have any other comments or questions around the table?

DR. ALLEN: Mary Allen, Center for Vet Medicine, Office of Research. I just wanted to comment on your last point, what emergent technology is on the horizon and generate big data. We are at the Center for Vet Medicine not only in the Office of Research, but in the Office of Drug Approval, where we approve drugs for animals. We are faced with huge amounts of data that come in, not only from the drug companies, the sponsors who want us to evaluate their data, but we in our antimicrobial resistance operation called NARMS at the Office of Research, we generate -- we continue to generate more and more whole genome sequence data, and now we have more modern mass specs, which are data, generate voluminous data.

So this little 168-acre campus with no connection, literally no connection to White Oak or the

Wiley building, so we're at a real disadvantage to process those data, manipulate those data, or store them. So I am with you, saying that we're going to see more and more of the need for handling large data and we've got -- FDA has got to be ready to do that, I think. We don't think we are. We're isolated, so we're a special case, I guess, but I think we're all going to need huge capacities in the very near future.

DR. TONG: Thank you. Thank you for brought me to attention. I think I heard about this, but never really sink in, but definitely we need to talk a little bit more, see how can we help.

DR. ALLEN: Thank you.

DR. SLIKKER: This is Bill Slikker, NCTR. We want to be your partner, okay? We have the opportunity to reach out to all of FDA, and we have done so in many cases, but all we need is just an opportunity to talk and discuss these opportunities with your staff, try to figure out what the best solution is, because oftentimes either we can build bridges through electronic media or other approaches to try to solve problems together. We find it much more useful, as you well know.

So we want to be your partner, and I'm glad that you're here to reach out and to understand some of the

possibilities that we can generate together.

DR. ALLEN: Thank you. I look forward to it. I am learning a lot about the challenges that some of the rest of us face, too. Thank you.

DR. SLIKKER: And along that line, some of the challenges -- and I think there's been a theme here now this morning about filling positions, and it isn't as if we do not have something to offer at NCTR, FDA, in general, but it's not as though the NCTR is alone within FDA about filling positions. But I must say that we need to think about processes and approaches that are appealing to individuals that want to do research, and one thing that hit me is that we ought to really be advertising the optimization of working for the federal government, especially within the FDA. We ought to be talking more about this, and FDAers are kind of quiet, they don't want to make a big splash, you know. We're sort of conservative folks, but if you look at the accomplishments that have been made by FDAers, it is truly remarkable. After all, the Society of Toxicology, which is now 8,000 strong and the largest society of its type in the world, was founded by FDAers. Just one example.

There's many, many others of the kinds of accomplishments that have been performed by FDAers, and yet

we don't oftentimes talk about that strength. It's almost as if the leadership is afraid to talk about how good their people are, because obviously then they could be recruited by others.

(Laughter.)

But the point is that we really ought to be talking about the opportunities that working for the FDA, and if you look around this room, you're going to see many people, including myself, that have been here for 40-plus years. There's a reason for that. This is a damned good job.

So the people have to understand, and we don't want to keep it a secret, that it truly is good to work for the FDA, and we have to make that more clear to people around the world. And we have to find ways to work within the constraints that we have, now based on the fact that you have to be here three of the last five years to be considered. That is a real liability that has to be dealt with, and we have to figure out some way to deal with that particular liability.

The last thing I want to mention is much more focused, and that is that I'm not sure that our new director of communications is here, Tonya -- is she here? Is Tonya here?

There she is. Okay. I failed to mention it earlier, because actually her whole position became available and was filled during this period of time between when we originally scheduled this meeting and now. But she is responsible for coordinating these efforts in terms of the slide quality and also in terms of meeting the 508 compliance that we have to meet, which is a real pain in the neck, but we have to do it.

The point is I just wanted to mention that she is one of our folks that just filled this position. We're very proud to have her in this role of chief of communications for NCTR, and all the linkage that makes not only within the NCTR, but between the centers of FDA and to the outside world. So we appreciate her efforts and her help and welcome her to this new role.

So that's all I have. Thank you. Turn it back over to you.

DR. ALLEN: Just have one more thing relative to how do we recruit people for these many positions. I am a big advocate of STEM activities and we have a festival in Washington D.C. every two years. Not we, FDA, but it's a nationwide festival, and I think that we have to start thinking bigger about not just the immediate vacancies we have, but 10 years from now, and if we don't start really

paying attention to STEM, I think we could be in a worse situation than we are now. So I'm all for advocating for this for young people.

DR. LEIN: Any last comments?

All right, I believe we are adjourned for lunch. I will turn it over to Donna in a minute to tell us any logistics about lunch, but we are to reconvene at 1:15, at which point we will recommence with the overviews from the NCTR directors.

DR. MENDRICK: This is Donna. Hope you've paid for your lunch. Should be available. One thing I did want to remind you is please sign in if you haven't done so already.

Thank you.

(Luncheon recess.)

AFTERNOON SESSION

Agenda Item: NCTR Division Directors: Overview of Research Activities, continued

DR. LEIN: -- about the Division of Genetic and Molecular Toxicology. Dr. Robert Heflich.

Agenda Item: Division of Genetic and Molecular Toxicology

DR. HEFLICH: My name is Bob Heflich, I'm the Director of the Division of Genetic and Molecular Toxicology. We have a Deputy Director in our division, Mugimane Manjanatha. He is here. So as many of you know we're going to be reviewed in depth at the end of this meeting, starting 1:00 tomorrow, so this will be an overview that hopefully won't be too redundant with what we do tomorrow, at least that was my intention. And of course, we have the slides that we go through that Donna gives us the format for.

Our division tends to be fairly consistent. Like the rest of NCTR we have about 30-35 people more or less on hand at any one time. We increased by five from the year before because we lost a lot of people in 2017. This has 34 staff members here but actually they're 33. During the furlough one of our staff was transferred to CEDR, so we lost her, and she turned out to be kind of an important

person to us because some of our sponsored studies with CPT kind of relied on her, so we're trying to decide exactly how we're going to handle that.

Anyway, 33 at present. We've got about 12 PIs, and we have about an equal number of support scientists. I'd like to have each PI have some kind of support, either a support scientist or a ORISE post doc, or both if they justify it.

Myself I have two senior support scientists, which is GS13, and they tend to have very high level skills and I tend to assign them to different projects as needed. One of them, Ying Chen is very good at molecular biology, so she is working with Xuefei Cao now on doing some micro-RNA analysis. And she's also working with Megan Myers on doing some DDPCR analysis.

So in theory I like to use those two people that way as sort of floaters. Okay, so DGMT outreach. This is a very brief summary that if you stick around you will get the full treatment as far as listening to all of our collaborative projects within FDA, within the government, within academia, and internationally. Each one of you who stay will be given a big book to peruse through.

So one thing I didn't mention here is our academic collaborations. We have very strong current

collaborations with the University of Arkansas Cancer Center looking at pig-a mutations in a group of head and neck cancer patients that have been treated with a mutagenic chemotherapeutic agent. We also have a very good relationship with the University of Maryland Medical School in Baltimore, their pharmacy department, and they host a website for us for nothing, so good deal there.

As far as global outreach, these are some things I put down that I know about. HESI, I think you know what HESI is. If Dan Acosta was here I'd have to explain all the acronyms to him. IWGT is the International Workgroup on Toxicity Testing which meets every four years, and OECD I'm sure you know what that means.

We have leadership positions on committees in each one of those,and participate in a lot of their workgroups. We've had people who are regional SOT officers, not nationals yet, and EMGS we've had presidents of EMGS and secretaries over the years, over the last ten years anyway. So we're fairly active in our outreach activities.

As far as our interactions with FDA, I'm not going to go into them in any detail, but currently we have very strong relationships with CEDR and CTP, and we're gaining a relationship with CBER, which I hope will be fruitful in the near future.

Our mission is to improve public health by providing FDA with the expertise, tools, and approaches necessary for comprehensive assessment of genetic risk, and our goals, which I inherited from the last division director will respond to agency needs for chemical specific data. In recent years that has been nanomaterials, tobacco products, and drug impurities. Maintain our tradition of leadership in regulatory assay development and validation.

Those of you who are familiar with gene tox assays which are important to FDA regulation decision making will recognize the fact that my predecessor, Martha Moore, sort of developed a mass lymphoma assay as a graduate student, and she stuck with it throughout her 45 year career, to the point where one of the last acts was to write an OECD test guideline, a separate guideline for the mouse lymphoma assay. I'm presently working on an OECD test guideline for the pig-A assay, hopefully that will happen before I pass on.

And the last point is establish new paradigms for regulatory decision making. And this is sort of a catch-all I use for our original research efforts that might not be specifically something that FDA asks us to do, but which we feel will benefit FDA and the field of genetic toxicology in general.

PARTICIPANT: Our strategies are, number one is to engage FDA product centers, NTP, and other national/international organizations to set our research priorities. I think we do that with FDA, sometimes it's a little difficult. We are members of all the right committees and everything, and we try to read all the guidances. This is as bad as NTTR, this is the kind of interference we get there. It seems short enough to me as it is.

But in general it's difficult to do that, for me anyway from Arkansas, because it is a distance. I heard some people saying face to face is still the best. And I have some longstanding, or we have some longstanding interrelationships with people, especially in CDER and CFSAN, and we tend to get a lot of information through them, perhaps more than from formal interactions with committees. That's important I think, experience does pay off sometimes.

The next two points are general research priorities currently that I've sort of singled out that we're trying to make some headway on. First of all develop better biological models for assessing human risk, and I'll tell you something about that in a minute. And develop more comprehensive approaches for monitoring genetic variation,

and I'm going to tell you about that also. And I'm not going to tell you about evaluating data to determine human risk, because that's going to be somewhat esoteric for most people who are not familiar with gene tox.

So some of our top accomplishments, and these kind of accomplishments are areas, I've used the term loosely here. One of the big sort of projects within the division, and this goes back about ten years, you may or may not be familiar with the pig-A gene mutation assay. It was invented or revealed at NCTR in the mid-2000s, co-invented I should say with another commercial outfit who independently came up with the same thing, and since then we've sort of worked together in building regulatory acceptance with it.

It's a very nice gene mutation assay, it fulfills a niche that I think most people appreciate in that it requires very small samples of blood, peripheral blood, like a couple microliters, and you can measure mutant phenotype in erythrocytes doing that. There are a lot of erythrocytes in a microliter as you probably know. So you don't have to sacrifice the animal, it's very three Rs friendly, which OECD likes of course for an in vivo assay.

And one of the obstacles we've come across to full regulatory acceptance, and the way we've been doing

this is the straight line OECD pathway of going through the steps and getting a test guideline at the end, which is important in a lot of jurisdictions, maybe not so much in FDA, but it's important in a lot of regulatory jurisdictions, is to go through all the steps of validation and test guideline development.

One of the requirements is to show that the assay measures what you say it measures. And we're saying it's an assay for pig-A as a reported gene, gene mutation. Okay, not so easy to do when you're dealing with erythrocytes, which is one of the reasons it's so nice to use, because you can just take a little bit of blood and do the assay.

So what we've been doing at NCTR as far as research is concerned is the mutations that cause the mutant phenotype, if it's really pig-A, occur in adult animal sin the bone marrow. That's where erythropoiesis and generally speaking hematopoiesis occur. So we've been sorting our ways through all the different lineages of bone marrow cells. They all have nuclei.

And looking, using some fancy sorting and antibody identification of cells, and some fancy sequencing techniques that if you stick around for tomorrow you'll hear all about from Vasily Debrovolsky. We've gone through all those and shown essentially that when you get an

increase in mutant frequency in erythrocytes you see an increase in mutation frequency in the precursor cells for the pig-A gene.

Here's another top accomplishment, and this is Barbara Parson's work, along with her colleagues Megan Myers and Karen McKim and Kelly Harris. Over the years, I should start out from the beginning, we've been very interested in methods to look at sequence variation directly without using a phenotype. So you can imagine how useful this might be for mutations that are not easy to measure phenotypically in the short term, like mutations involving causing cancer.

So Barbara over the years has developed methods to directly measure mutations in cancer, what's called cancer driver mutations, which are arcA genes and tumor suppressor genes generally speaking, and relating that to tumor induction both in humans and in rodents. And the idea is to develop some kind of a mechanism whereby we might streamline the process of evaluating the tumorigenicity of regulated substances.

So here is just a look at this, is a recent observation that caught my eye. Barbara has put a lot of data together. You might know that cancer driver mutations, mutant frequency in normal tissues is quite high related to

what you're familiar with reported gene mutation. So it could be in the one in ten to the fifth, up to one in ten to the fourth, even higher. But what she has found is that it's the variability between samples that actually is important for whether or not that cancer driver mutation will participate in the tumor to eventually form a tumor.

And this is shown in human tissues for various types of tumors, it seems to be independent of the tumor, and it fits in nicely with a current theory of carcinogenesis, which most people are not aware of but I think they should become aware of because the Vogelstein model, you can forget about it, it probably doesn't fit the present day data.

And I commend you to come back Thursday morning and listen to Barbara. If you can follow what she's saying about the models and how mutations participate in tumorigenesis I think you'll be happy you stayed around.

DR. MENDRICK: Bob, I have to interrupt you for a moment. This is Donna. He keeps talking about a meeting Wednesday afternoon and Thursday, that's actually a closed meeting, the public cannot attend.

DR. HEFLICH: Is there anybody from the public here? I'm sorry, public. Okay, so this is a bunch of projects I put under one rubric. And what you see here is

data output from a comet assay using a technology called the comet chip, which was developed by Bevin Engelward at the MIT, and that we've been using for the past year or so, and it's really great.

I must admit it really improves the data that you can get out of a comet assay. And the way this thing works, it's a, I almost brought one with me, it's about the size of a 96 well plate, and it has 96 positions on it. Each of the 96 positions has 400 micro wells in it. And each micro well is big enough to take one cell.

So if you put the right concentration of cells into that well, of the 96 wells, and you let the cells sit down, they'll find a position and they'll be nicely arrayed. And what this gives you is a lot of cells to look at, for one thing, that you don't have to look at manually. And it enables the automated image analysis software to score these things very easily.

So with this kind of thing, a 96 sample experiment, you can think of all the treatments you can do in 96, plus the 400, you can do a very dense dose response kind of analysis. And the data is very tight, you can see how reasonably tight it is when you separate out the cells nicely. So this is really a nice technology, and Bevin should be congratulated for coming up with it.

So we've used this in a bunch of projects. Mangeo(?) has developed a version of the comet assay to look at epigenetic effects. Shou Chain Yow(?) looking at primary human hepatocytes, and the HepaRG cells, you might be familiar with those, and that's sort of a loose collaboration we have with the people at NIHS. And we're using it with multi-flow technology also to get a handle on the mechanism of action that's going on. So as I said, and it theoretically could be used for in vivo, although we haven't done that yet.

So third, number three here, is something that I've been talking about for a number of years. And this is our interest in developing human based tissue models for use in toxicology assessment. And the model that we're furthest along with is a model for the human airway. And up here on the top you can see a cross-section of a tissue. That's actually a cross section of an in vitro tissue model of a human airway. It's got all the kinds of cells that you would see from the large airway portion of the bronchial tree.

And the interesting thing about it is if you grow it correctly and if you differentiate it correctly, I should say that these cells are taken from human autopsy material from humans, and you sort of mash up the lungs and

you plate them out and then you give them the right signals and the right kind of media, and after a month you've got something that looks like this. It really has the structure and also the function that you might expect from the human airway. So it has been very useful.

Anyway, we've used this, and you'll hear more about this to come, to develop a number of toxicological endpoints. And you can see some of them listed here. The culture produces mucus for instance, and the cilia beat, and you can measure cilia beating frequency. But we've never really done any kind of gene tox endpoints. So one of our goals in the next couple of years is to develop some gene tox endpoints to add to this.

And one of the elements to this is we've got a free (inaudible) that's exposed to the atmosphere. So presumably if this is an inhalation model we can expose the cell cultures in a way that's consistent with how the airway is exposed in vivo. So these are a couple pieces of apparatus we have that do just that.

Finally, I'd like to talk about another area of emphasis, and that's looking at mutations directly using next generation sequencing. And there's a number of angles that people have developed that can do this. This is one of them that Javier Revollo in our group has developed for

looking at clonal variation, which uses the power of developing a -- from treated cells to amplify the mutant signal, so their standard kind of error corrected NGS will be able to measure very rare events under those circumstances.

So he has applied, and we have applied this to various circumstances. When you can make a clone out of a cell you can probably detect mutations in the whole genome using this. And with bacteria it’s really easy, you can put lots of them on a single flow cell and get lots of data out of it, very economical too.

So here are some new projects. And I told you about developing genetic toxicology endpoints for our in vitro airway cell system. There are a bunch of other things that we have given a try at various times and that were considered, and we can discuss this during our subcommittee meeting, including making a rodent version of this. What we’ve been working with is a human version. Much of the tox data is in rodents, in rats. So it would be nice to have a rat version of it so we can validate the endpoints versus in vivo very directly.

Another thing we’re thinking about in this tissue model area, more than thinking about it, developing, is a testicular organoid system, and you can see here’s an

example of an in vitro organoid that's been developed in culture versus what looks like in vivo, and this is stained, the orange is Zo-1 staining, which is for tight junctions. So you can see it's reasonably similar.

And supposedly this organoid would go through all the germ cell developmental stages for the male germ cells. So this is really interesting and it has already by word of mouth gained some interest in the FDA as far as other people wanting to try out their problem using this.

And in the future I would like to make more use of computational modeling techniques. This particular one uses a technique to describe the distribution of aerosols within the human bronchial tree. And you can see the red means high and the green is low, and you can see how it varies from place to place.

So if you want to get a handle on dosimetry in vitro versus in vivo, you need to look at this kind of data to be able to do that, besides doing PK type of studies. So we've done a little of this but I'd like to be able to do a lot more. We do have the software to approach things like this.

And I have to add this also, Barbara is very interested to take some of her data, some of her cancer driver cell mutations data and model that quantitatively to

predict tumor outcome. And I think there's a lot of potential there, some people have done that in the literature, just a few people, but I think this is a field that's emerging and could be very useful for FDA.

So I think I'll stop there, I wrote down a couple of questions. But if you have any questions please let me know right now or else I'll have to read my questions which are pretty trivial and were thought of five months ago. Okay, thank you.

DR. LEIN: Thank you Bob. Are there any questions from the SAB? Comments?

PARTICIPANT: Chuck Casper, SAB. What precautions do you take in your error correction on your next generation sequencing? And do you account for assembly errors as well?

DR. HEFLICH: There is certain criteria we put on the data. It's pretty conservative. This is way over my head as far as the computation assumptions we make. But essentially it catches the tip of the iceberg. I mean when we look at mutations, to be able to convince ourselves that the mutation is real we have to see it more than once in paired analysis. That's a major sort of a requirement.

I'm sorry, I'm drawing a blank on the rest of it. Is there anyone here who might know? I don't see any DNA

sequencing people here unfortunately. But Javier Revollo is going to give a talk, as well as Vasily Dobrovolsky is going to give a talk in pig-A where we've used this technology to analyze mutants, and they will be much better able to answer your questions as far as the details of it are concerned.

PARTICIPANT: With regard to your question about should we place more emphasis on microphysiological systems, can you just tell what type of emphasis have you placed on it and what engagement have you had within the centers around it?

DR. HEFLICH: Well there are all sorts of tradeoffs here. Obviously microphysiological, you like to build a human kind of in pieces, and that has a real attraction to it. But every time you add something to the system you affect its stability on the long-term. So this particular system that we have here, we remain in steady state for about a year, and you can theoretically, even though it's just the site of contact kind of reactions, you can do repeated treatments, and we've done that, over the period of a year.

Now we can add cells to that, you can add endothelial cells, you can add immune cells to it to produce a more complex kind of response. But every time you

do that those cells are kind of going off their own way, and the system itself gets out of whack after about a week. And the same thing happens when you use more than one tissue and you kind of link them together.

Now, one of the requirements I think for the new microphysiological systems is that they be able to maintain themselves for a month. Now, that's a pretty tall order actually with many of these things, because they, using one media to pump around these things, and keeping all the cells happy and in a steady state over a month's period and functional is really a difficult thing to do.

So my feeling is okay ultimately what we're doing here is developing a test that one of our sponsors could use for evaluating their products. So we would like to keep it simple so not only we can do it but other people can do it, and it can give us an output that we can relate to a biological response. It might not be the full extent of complexity, but at least it will be information that we can use to make a regulatory decision on.

So we have decided to stay here with this very simple model, which has been around for 10 or 15 years, and we sort of adopted it. But philosophically you can look at this differently. Now we have an MPS system that enables us to take our airways, and we can treat them using our

sophisticated exposure systems and pluck it down in the MPS system where the liver or something like that goes on.

One of the problems with airways is the closed MPS systems don't enable you to treat them as you would these open systems. That's another consideration. We've got that, and we'd like to try it with just a two tissue system and see what kind of data we get. So I think we're approaching that very carefully.

I mean we've got something here that I think is good and valuable, and I'd like to develop that and see how much information we can get out of it. The potential to add onto it is certainly there. I look for perhaps doing that in the future. So, any comment on that philosophy for one thing? I know it's counter to a lot of people's philosophy who like to think of everything, seven different organs on a chip kind of thing, but I think that's a real difficult thing to do.

PARTICIPANT: My question relates actually back to some data that Fred referred to earlier with the work that NCTR has done on acrylamide and glycidamide we've seen DNA damage in organs that do not develop tumors. Is that work being carried over into your division? Is that related to the cancer driver mutation kinetics to try to understand that better, like why would we see DNA damage that's not

associated with tumors in some organs and is associated with other organs?

PARTICIPANT: No, in a word. We haven't gotten to that degree of interaction. Most of our work in this particular system, the airway system, is done specifically for inhalation type exposures, and we've worked with CPT which had been with us since the very beginnings of starting this, and more recently with the NTP, who have a protocol they'd like to see us work through so that they can decide whether or not they want to use the system for kind of prioritizing their problem chemicals.

So we're sort of aiming at particular goals. I didn't want to really get into that because that's sponsored work and we really, your suggestions and comments, while valuable, would have less impact on that kind of a situation than the NCTR projects which we're very flexible about and we can change up if we hear a good idea.

DR. LEIN: Any other comments? Okay, thank you. Our next presentation will be by Dr. Carl Cerniglia, Division of Microbiology.

Agenda Item: Division of Microbiology

DR. CERNIGLIA: Good afternoon everyone. It's always quite an honor for me to participate in this meeting. I've done it a number of years, I'm one of the

ones that Bill has mentioned has been around a while, but it's always great for me to have this opportunity to represent and lead the division, and give the overview of the program amongst a distinguished gathering of scientists like yourself, who as you know I really sincerely appreciate the time that you all spend here amid the heavy burdens and professional duties and responsibilities that you have at your various institutions. So thanks for that. Especially during Spring Break, you may have even been pulled in directions taking family and kids places and maybe couldn't necessarily do it.

I thought I'd start off quickly, Dr. Slicker did a great job of giving the history of NCTR, but what I'm going to do is just slightly deviate a little bit and go backwards a little bit in history, because the roots of the Division of Microbiology actually started very early in the biological operations phase of where we're located, was part of the Pine Bluff Arsenal, was called the Directorate of Biological Operations.

And in the '50s and the '60s from a microbiological perspective they were very active in producing seven biological agents. And they had a world famous microbiologist there, who was an Army captain, Dr. Patrick, who was one of the first to actually aerosolize

bacillus anthraces spores that they could weaponize. And so that was our history.

And the reason I mention it too is because while we had microbiologists down there, about 30 miles from here, and those microbiologists were fantastic in diagnostic microbiology, very well skilled, you can imagine working with those kinds of agents they were well skilled.

So when we converted over to the story that Dr. Slicker was mentioning, how we got from there to where we are today, we carried over those microbiologists and we utilized their skills as diagnostic microbiologists in the surveillance program that we have ongoing at NCTR since that time to the present to monitor the animals to make sure that they're pathogen free so that the investigators when they're doing the kinds of studies that you've already heard today are good to go from a microbiology perspective. So that's a little bit of the history.

And actually I arrived in 1980, and this was not mentioned this morning, but I think it's important too to mention the fact that we're part EPA and FDA in our origin, and about 20 percent of the budget was EPA, and actually I was recruited for two reasons by Dr. Fred Calibar(?) for my experience in environmental bioremediation, because there was a lot of obviously the breakdown, using bacteria and

fungi to create hazardous compounds was part of our mission at that time, one of the aspects of it, and the other aspect is having formal training in anaerobic bacteriology to get intestinal, looking at the role of intestinal bacteria in the metabolism of xenobiotic compounds.

At that time we were focused mainly on metabolism, and they had studies on benzamine, azo dyes and also on nitro polycyclic aromatic carbons, among other things. And so I was very active in that aspect of the program as well. So that's how our roots came to where we are today.

And the program has evolved from that point to today based on these kinds of committee meetings that we're having today, getting feedback from people like yourselves and actually incorporating some of these things, and I'll mention that. So I just kind of wanted to start off with a little bit of a history perspective for those who are not aware of it.

In terms of the numbers, similar to if you consider the microbiome, if a healthy microbiome is stable, so is our workforce over the years. We've had about 26 FTEs, it hasn't changed much. We have one vacancy now which we're recruiting which is at the support scientist level. In contrast to what Bob just mentioned, you saw his ratio

of research scientists to support scientists, we're not identical but quite close. In our particular case there's more PIs than support scientists.

So in discussion with my staff when we had an opening we decided to go to support scientist route, so we're in a process now of recruiting. So that would be at the bachelor's level or the master's level. So if anyone who you know is interested the announcement is not going out yet, so we'll be advertising for that.

Also our numbers kind of vary, we have a total of 34, it can go upwards, as high as 40 to 45 depending on the visiting scientist program and the training program at the division. I have a great staff, and that's one thing, people are important, that's what it's all about, and I'm very proud of the staff that we do have, it's an extremely talented staff to meet the needs of the FDA, and they're very very good at mentoring. And so over the years we've been very active as a group in the visiting scientist program and the student programs, and that brings up our numbers even higher.

In terms of outreach I won't spend a lot of time on this because you've seen these kinds of things from the other divisions as well, we're very active with all the FDA centers. We have the active protocols. The only one which

we don't have an active protocol that we're just finishing up studies is with the CPT, we have had two projects with them which aren't done now but we're still in some cases writing up the manuscripts, and I'll talk about one project later. We also have projects, the National Toxicology Program, many of the other federal agencies, local health department, universities, and our global outreach is wide.

Personally I'm very active in the World Health Organization with the JMPR and JECFA in food additives and pesticide residues, and some of my other staff are very active, and I won't go into this today, but certainly if you have questions later about our specifics on any of these involvements I'd be happy to give it to you, but I'd like to keep this tight and on time as possible.

So the mission of the division again has been shaped over the years, but basically we serve a multipurpose function with specialized expertise to form a fundamental and applied research in microbiology areas of FDA responsibility, toxicology, regulatory science. So we're one of the six divisions here, and most of our projects that come out have been developed in an exchange between our FDA centers and liaisons and scientists as well as advisory boards like yourself, and grass roots from the scientists within the division.

So our strategy, mine is a little bit different than kind of what you've seen from the others, because I like to start at the strengthening and research management, so it's going to be bottom up when you look at this, so you have to have a strong foundation. So I've put a lot of effort into trying to strengthen research program, administrative and research management depending upon obviously it's certainly budget driven to a lot of extent.

But one as I've mentioned too, we have an early history, coming with that early history in micro we earn the oldest buildings in NCTR, so these are the original buildings that were used way back when, they're still present, although they've been updated, but still we urgently need at some point to have a modern facility.

Just like you I serve on science advisory boards, I'll be at Clemson next week, and it's always nice when you go to these things, you see these beautiful life science buildings and all these modern things, and I say oh boy I wish we had something like that. But we don't. But anyway, that's another question. I know we're renovating, we're doing the best we can, and people are moving into some newer facilities, and that's wonderful.

The other aspect, which is important, is having benchmarks, if you want to get research (indiscernible) you

have to have benchmarks built in, and we have that and I can discuss that later. I think it's very important to have meetings like this, how we can enhance our FDA research interactions. And ultimately our goal is to contribute to FDA guidelines and regulations, and we have several examples of that which I'll be talking about.

Again, in terms of the research areas, it's kind of lumped in this particular slide on five bullets. If you go from top to bottom it's of degrees of importance or numbers of studies. The first bullet is more on the impact of a wide variety of agents. FDA regulated products on the microbiome, and we have a number of studies where we're looking at these types of interactions, and I'll give you a couple examples of that.

The other area which we've really expanded over the years is developing methods to detect and characterize microbial contaminants and FDA regulated products, and I'll give you some examples of that. In terms of food safety we've always been doing work in the food safety arena, but we've shifted pretty much now to pretty well focused on mechanisms, more on determining antimicrobial resistance and virulence mechanisms of foodborne and other pathogens.

Years ago in earlier times we did a lot on detection and surveying and just cataloguing antibiotic

resistance genes, and now we're looking more at the mechanism of that. And there are reasons for that, and I can explain later. And we're conducting research in areas of women's health, tobacco products and nanotechnology. And we've always done quite a bit in risk assessments, especially from a systems biology perspective.

I kind of pride myself in over the years modernizing, even before we had a systems biology program here at NCTR we were actually doing systems biology, producing some of the first papers at the institute actually on proteome analysis, et cetera, and many of the other types of techniques that currently we use in system biology approaches.

Again, as was mentioned by the other division directors it's pretty difficult to list the top three accomplishments over the last five years. I think the program, as I've said I'm very proud of the staff and what they've achieved. There's a number of them, so I'm just going to hit the high points of these, and instead of just repeating what's on this slide I'll go right to it to save us time.

The first one is more of a food safety initiative, and this is led by Dr. Steve Foley, and basically the central hypothesis of Steve's and his staff's

work, and when we're talking about salmonella enterica which as you all know is a predominant major food born pathogen, but what his central hypothesis is essentially is looking at salmonella virulence and antimicrobial resistance associated plasmids encoding factors that play a role in colonization and persistence in food animals during infection process in the human host.

So he sets his hypothesis and then he has these various study objectives. And this particular work has been in collaboration with scientists from the Center for Veterinary Medicine, both at ONADE and also at the Office of Research.

And I'll get right into, instead of going into each bullet point, because I have those bullet points on the next slide basically where we're actually looking at the accomplishment, and what he has demonstrated is that certain antimicrobial exposure, especially we're going at the low dose levels, tetracyclines and chloramphenicol impact plasmid transfer dynamics in a dose dependent manner. And this is very critical, and he's doing this work both in vitro and in silico approaches.

He's evaluating the dynamics of the host immune responses to infection by strains containing these virulence determinants and trying to link these using both

human and animal cell line study. So it’s pretty interesting work, and he has focused a lot on this in compatibib(?) plasmid, which encodes factors that likely contribute to infection under low iron conditions.

And we know that iron is very important for these bugs, acquiring iron for growth and potentially causing infection. On the other hand, it’s also very important in the host response as well, in innate immunity. So there’s push and bull between iron in the GI track and exposure to salmonella’s role in this.

He also evaluates in these plasmids the role that bacteriocins, which are compounds that are antibacterial in nature, so you can understand why an organism like salmonella would produce these types of compounds, so that they could outcompete the commensal bacteria, so then you’d have an overgrowth issue.

So he’s studying again, using both the wet laboratory and bioinformatic approaches, these interactions. And he’s going to continue this, and later, I’ll give you the punch line even later, he just received an Office of Chief Scientist Challenge Grant with CBN, and he’ll be looking at this in a more in depth way as well.

Another important project is detection of microbial contaminants, including pathogenic mycobacteria

in tattoo inks. And Fred Beland mentioned a study that will be going on in tattoo inks. Tattoo inks can cause, there are potential adverse effects of tattoo inks. About 29 percent of the population over 18 years or older have at least one tattoo, and one of the issues we're a little concerned about is the actual ink itself being contaminated with microbes.

So this is before it's actually being applied, a lot of the adverse health risks related to tattoo inks could be just getting infections due to unsterilized processes, when you're getting inked, or as Fred was alluding to when it's on the skin, getting absorbed, that type of issue.

In our particular case we're looking at the ink actually before and seeing exactly if it's sterile or not sterile. And the reason for that is that there were a number of recalls. During the last several years over 70 recalls were made by the USA on tattoo ink related things.

And this mycobacterium project was one in which mycobacterium chelonae which causes abscesses and skin infections, it was shown there was an outbreak of that. So with that a red flag went up and they asked us as well as LRA regional lab out in California and also a contract lab to evaluate tattoo inks for microbial contaminants.

And in this particular project Dr. Sanjai Kim and his team in my program are looking at these inks, and they surveyed over 85 unopened bottles of tattoo inks and also permanent makeups purchased from 13 different companies, and basically about 49 percent of the inks were contaminated with microorganisms. It can range from as low as 10 to the third all the way up to 10 to the eighth, depending on the ink.

Some of these particular, when we actually did, and we were doing all the belt and suspenders type of identification, doing culture techniques as well as our TPCR techniques, and then certainly sequencing to identify these organisms. And some of them have been reported, the ones we've isolated, some of them are reported to be potentially associated with skin infections.

So with this there's been, with CFSAN, Nakisa Sadri(Phonetic) and Nissan Moon(phonetic) were the leads that we're working with in CFSAN, and they were very pleased with the work that we're doing and they fully fund and support, and we're doing follow-up surveys at the moment. They've asked us to do even more work, so we're collecting more samples looking at these, and they also asked us to look at endotoxin levels as well as these particular inks. So this has been a very interesting study.

And this is an example, when I talked about impact factor this is an example where some of the work that we've been doing has led to potential recalls from four companies. So this has impact, this particular work, and we're continuing to do it. We have conference calls almost on a weekly basis on this subject.

On the microbiome area, and Dr. Slicker mentioned this as one of the emerging areas in his opening, obviously I think, boy on TV you've got the skin microbiome examples, or the probiotics. So it's both in the public press and in the scientific arena. So it's certainly one of the hottest areas and it's a very important area.

So we've been involved in this as mentioned earlier for a long time in various aspects of it, and we have projects, microbiome related projects on almost every clinically anatomical site. Skin, vagina, Office of Women's Health projects, certainly with NTP it's been focused on the gut microbiome. With CTP it's been oral microbiome, and so we have a number of projects in that. I'm just going to go over some of these relatively quickly, and again instead of reading these I'm going to go right to the actual accomplishments so we can move along.

The issue of antimicrobial residues in foods is one that is a very important priority for the Center for

Veterinary Medicine in its impact on the human intestinal microbiome. The use of veterinary antimicrobials in food producing animals may result in more than negligible or trace amounts of drug concentrations in the edible food supply if the treated animal is not being adhered to the actual withdrawal times and the other practices that are put in place. So there is always a potential for residues in food.

So we've been, over the number of years, there are four fundamental things that we want to know. One is are these residues in food bioavailable to the GI tract. Two, do they impact the bugs in the GI tract. Do they select for antibiotic resistance. And fourthly, do they impact the intestinal cell and permeability barrier. So we've been addressing these questions with three different compounds, enrofloxacin, tetracycline and currently erythromycin, I'm just showing you the data here for tetracycline.

And bottom line is that the levels that are set, these low level residues that are below the acceptable daily intake values that are set for tetracycline's 25 micrograms per kilogram bodyweight per day, we do not see impact in that. In fact it's very interesting these things bind very quickly to the intestinal contents, and they do

not desorb and they are activated relatively quickly.

But anyway we're doing a lot of studies using the most current technology. And you heard Neal give an excellent talk on nanomedicine and nanodrugs and the importance of that. The interesting challenge to us is looking at the effect of these, we're doing comparative studies between the parent compound and the nanodrugs and seeing what impact they have using both in vivo, ex vivo, and in vitro models.

And basically, as Neal was mentioning today, these nanodrugs have very specific properties, and certainly they can increase solubility and absorption, specifically in the GI track, they can persist longer, they have many benefits and we're more interested in knowing those interactions in the GI tract. This is a collaborative project with CDER and also with the NanoCore facility, Dr. Gukolon(?) is leading that effort.

On the oral microbiome project we have a project with Center for Tobacco Products, and in this particular area it's a very interesting study because we work not only getting the predominant organisms in the oral cavity, similar to the GI tract there's a lot of bacteria in the oral cavity as you can imagine, over 700 different species, and the numbers can be extremely high, anywhere from 10^6

to 10^10 organ per gram tissue, so we're looking at those interactions of what happens to the oral microbiota because they're very important in oral health, maintaining a balance in oral health.

And we also did a study in collaboration with CTP with the biochemical toxicology program in their cheek pouch carcinogenesis model with the Syrian golden hamster, and that was kind of neat because they got the smokeless tobacco product right in the pouch, just like you would be using if you were using snuff or chewing tobacco, look at those interactions, and basically there was an impact on that on a diversity, and these papers have been published.

On the microbiome as part of the NTP program, and this is a very important aspect, Paul Howard and I initially pulled together, we have Dr. Snygede Akar(?) in our program actually doing the laboratory research leading that particular effort, and now Don Calo(?) is very supportive in taking a lead on NTP with us, and we have Vicky Sullivan here from NIHS and Nigel Walker in those relationships.

So this is pretty cool, we're trying to see indeed if indeed does it really matter if we do get these low level residues. And we're talking, you saw the numbers even that Fred was giving for arsenic, giving the microgram

per kilogram bodyweight, or similar to what you find in residues in foods, do these truly impact the gut microbiome, this is what we're trying to get at, and we're trying to get at the methodology, we call good standard practice to do this type of research.

And I won't go into this particular project, we've spent a lot of time looking at arsenic and nano silver, the two major ones which we've done a lot of work on in other studies, and this is going to be part of a review of the national toxicology program in November, so I won't go into it today to save us time, but this is one of my pet subjects, and I'd just like to talk about the microbiome because I have my own biases between animal studies to human studies, and I can go on, I can give a lecture just on these kinds of subjects. So later, maybe with questions we can go into it. But I want to, also another important project, and this gets into the microbial contaminant issue, is this whole issue of contamination of pharmaceutical products with bacteria.

And the one where the recalls have been the most, and this is a project with CEDR, has been with Burkholderia cepacia. For those of you in the microbiota circuit years ago this used to be called pseudomonas cepacia, it has been renamed and classified.

Burkholderia cepacia is a very persistent organ that can grow, people say how can it grow in pharmaceutical water, distilled water. Well, they can grow much better in diluted environments than in the nutrient rich environments. And also we found doing genome sequencing it has resistant genes, and also for disinfectants that are in these products as well as biodegradation mechanisms to degrade these antiseptics like as was mentioned here on the slide.

So anyway, this particular project is an interesting project, they've asked us to develop a method, which we have, and they want us to use this particular method for this USP or pharmacopeia, they don't really have a method. The methods that they have are very rich environment and culture methods, so we have developed a method that can recover Burkholderia from dilute suspensions, and also resuscitate it so they can be detected.

We have three projects actually related to C. difficile. Two of them are related to fecal microbial transplants, and the other is to the diagnostics. And the fetal microbial transplant one is the project Dr. Doug Wagner is leading with Paul Carlson at CBER. And this has been a very interesting and challenging project.

What we're trying to do is look at the mechanism of how does FMT work. We know FMT is very effective to treat recurrent c. difficile infections. It could be anywhere up to 80 percent recovery, compared to other methods. Certainly when you're getting away from antibiotic treatments, this FMT is maybe a potential way to go, but we're looking at the mechanism.

So Doug Wagner is developing 2D and 3D models, and this is a very challenging study because if you're doing 2D and 3D models, and maybe sometimes even people are doing human cell work or animal cell line work don't appreciate if you're actually going to also have the microbiome involved, because then your tissue culture situation, you have to have the aerobic system to get those tissue going, but then you need the anaerobic condition to keep the anaerobic bacteria going.

So we have developed a chamber, Doug has, where we can do these kinds of models, so now we can look at this kind of competition where we can see c. difficile and the commensal bacteria and these human cells lines and then see what's going on. And that is what Doug is basically working on, and he's doing an animal study as well. And I'll just move on so I can get this.

Another aspect of this FMT which is a different

part of the problem, how does if you're doing fecal microbial transplant, I didn't define it but basically you're taking in feces, either through endoscopy, or a nasal tube, so you're trying to reestablish the microbiota.

So when you're trying to reestablish the microbiota, the challenge you have, a micro ecology problem of actually how the C. difficile interacts with the commensal bacteria. So we're doing bioreactor studies, and Bruce Ericson is leading that, understanding this interaction of between that c. difficile in interactions with the intestinal microbiota.

And the last project related to C. difficile is on the diagnostic end. This is when you go and you're potentially diagnosed with C. difficile. The first thing they do is you have to have a good quality fecal specimen, and that gets into storage conditions, et cetera.

Also you have to have the various test methods that are out there, whether it's the enzyme amino assay detecting the toxin genes or the PCR to detect that, there's different methods out there, and what CDRH has asked us to do is to actually design and evaluate some of these molecular methods that are out there. Also look at and evaluate the various ways in which these samples are stored.

There have been eight published reports, it's great, it's after lunch, on how the quality of fecal specimens are stored. So we're checking all of these and then doing ours and making our own recommendations, and that's the work that's going on in the lab with Dr. --

PARTICIPANT: So Carl, we're at the end of your time. Maybe you can wrap up the rest in about five minutes?

DR. CERNIGLIA: This is the challenge grant, I mentioned that before, that Dr. Foley has received, which is quite an honor for the NCTR and certainly the division, basically using both bioinformatic and wet laboratory tools to analyze plasma associating micro resistance. He's working very closely with the CDM on this. And that was mentioned earlier about NARMS, those people involved in NARMS and working very good with us on that.

So the future direction, and I can go through this relatively quickly, is the fact that we certainly want to enhance mechanisms of communication. This is one particular venue. Certainly we need to prioritize our research efforts, we've been doing that over the years.

We've really shifted tremendously, we've really broadened our portfolio to what it was before, but certainly we need to engage colleagues to do that even better. We want to leverage opportunities. We've done a

good job, maybe not as good as Fred was describing for his program in getting all that money, I wish he can lend us some, that would be nice. But anyway, we try, and we compete, and then it is what it is.

But anyway I give the staff a lot of credit for going out there and trying to do the job. We're going to continue on the microbiome, it's a hot area, so we're going to be moving in that area. So I think we have a lot of strength throughout our own program in that particular field, so if anyone is interested from the FDA centers and other projects we'd be happy to listen.

This whole microbial contaminants, this whole area, I think we're expanding in this. Fred mentioned about cannibus and he talked about the chemistry portion as well as the microbiology. The microbiology is being done in the division, and Steve Foley and his team and Jing Han are leading that aspect, working with Mary Pedro when that project goes online.

We have projects, it was mentioned about botanicals before, too. We have projects actually now in place on spices, evaluating imported spices, and other food ingredients and supplements for microbial contaminants. Ashraf Khan is leading that particular effort with CFSAN.

So we're going to probably continue to move in

that direction as well and continue also with the work that we're doing on the safety assessments using systems biology approaches. So with that I think I want to get the feedback, I hope I can leave time for discussion. So I tried to give kind of a broad brush of the projects, we have many things that we're doing.

I'll be here today and tomorrow, if anybody wants more details I'll be happy to provide it or I can just send you the information. I'd just like to finish though because this is very important. People are important here in every aspect, certainly the members here for being here today, again as I said thank you for your time, for the effort and advice and guidance that you're providing.

Certainly Dr. Slicker has always been encouraging, as well as the other members of the administrative for providing an excellent research environment for us. So I thank him for that and the team. And he's always giving encouragement and support for us, and obviously always keeping us informed with emails almost on a daily basis of the latest research and issues which I certainly and my team appreciates.

Without a doubt I must give special thanks to Donna for pulling this meeting together and taking it to fruition, it seems to be going along quite successfully,

and certainly the job that she does as our Washington office liaison.

One project that I mentioned with CDRH on the diagnostic methods for C. difficile detection, she was instrumental in making that connection as one example of others. And certainly I would be remiss not to end by acknowledging the unbelievable hard work and dedication of my staff. My presentation would not be possible without their help and talents. Thanks for your attention.

PARTICIPANT: Thank you Carl. Are there any questions or comments from the SAB?

PARTICIPANT: Steve Stice, SAB. Carl, I think there were two bullet points on your feedback request about how can we address the needs of the FDA centers basically, engage them further. I wanted to do what Pam did and turn the question around and ask you what are you doing currently to achieve those. That might help us understand better how we might help you.

DR. CERNIGLIA: Thank you Steve. It’s multifactorial. First, certainly we do the grass roots, the PIs in conversations with the various investigative centers, and sometimes that can go a long way, sometimes not, because the research interests of the individual investigators from the centers or from us might not be

truly in line with their center management or their time. So that's always something that needs to be considered. But it's nice to kind of generate interest from the grass roots.

Another thing that sometimes works and sometimes doesn't, and this was alluded to earlier about working groups, we have many on working groups, we're good at that within the agency, but a lot of times I noticed you don't get the feedback. They're on the working groups, but a lot of times in some cases the feedback doesn't come back, that exchange of information from these working groups back to get the research initiatives going.

I tell my own staff it's great for you, you have this information, but bring it back to the division so that we can discuss it more, and sometimes that works, sometimes it doesn't, but that's another aspect. Certainly then if you get to the office level as I mentioned, the Washington office level and Donna and those kinds of connections, sometimes that works, and doesn't in terms of the follow through.

It's tough, everybody is busy so you get the lead, you send an email, and then sometimes there's follow-up, sometimes it's like wow. Everybody is busy, including us, so how many times are you going to ask people for

things. I'm not good, I don't like to do that. If you ask me something once you'll get a response, I can guarantee it. But not everybody is like that.

Then you get at the Office of Research level here at NCTR, and the Director's Office coming down with making connections as well. So there are different levels, it's layered as I said, engaging within our own FDA centers. I think meetings like this if there's time can help. We have a science forum and that type of thing, we've been involved over the years.

It's still, I think the mechanisms of the communication, in terms of project planning and import to really do the high priority stuff, the pathway, it still needs in my opinion some improvement because it's very difficult for principle investigators, if we're asking them, we want to do really FDA impacted work as I mentioned in my strategies, sometimes it's very difficult for them to kind of go through some of these hurdles. So anything we can do to enhance that. I hope that helps a little.

PARTICIPANT: That helps. Not a new idea, but have you contemplated things like webinar type of formats where you could present capabilities to a broader audience of centers.

PARTICIPANT: Science program, I think seminar

programs are an excellent way of doing that. And Donna has even mentioned any time we're having a seminar to run it by her, once we get it out to put it as a webinar. What we are going to do in micro, and we're going to have a science day coming up at some point, so I don't want to interfere with that, but I have a plan, we already have a program together so our own division is going to have our own science day.

It's already done, we were going to do that, actually the date was during the shutdown, so we've kind of shifted it now. So actually that's a way of communicating, and maybe we can get that out. I have each principle investigator is going to be given what I call a flash presentation, so 10 to 15 minutes, and they'll be doing that. So that's already on the books, it's just a matter of scheduling a date now.

PARTICIPANT: Chuck Caspar, thanks Carl for a very nice overview. Following up on Steve's question, there's an enormous amount of sequence data and databases amongst various agencies and centers. How much partnering do you do at NARMS and CDC and these other agencies as far as sifting out the information from these huge datasets.

DR. CERNIGLIA: You're right Dr. Caspar there is a lot of information out there. This additional project here on database analysis that Steve Foley and his team are

doing, we're actually tapping into not only the NARMS program but actually the CDC databases. We don't want to rediscover the wheel either, there's things like there's Patrick and other databases out there that have this, so they're analyzing all these various databases to see indeed what needs to be developed or improved so that they can pull all this information together.

Patton McDermott and Shou Zou(?) are the two that he's working with at Center for Veterinary Medicine in this, and Pat leads the NARMS program for example, so we're pretty well in sync with that. And you're absolutely correct, CDC has a lot of information and we're working with them as well.

PARTICIPANT: They're willing to share?

DR. CERNIGLIA: it seems that way, yes.

PARTICIPANT: I have another related question -- I have several, but I'll just limit it to one. Related to your antimicrobial resistance transmission, are you looking at foods or environments that have varying densities of microbes, and that impact on transmission as well as the microbiome and transmission.

PARTICIPANT: For the foods program, the work that Steve and his team are doing, he's evaluating a number of different isolates of both clinical, human, and animal

isolates, and then they're screening a lot of those. So he's kind of looking at it from that approach. The organisms that he has obtained are either clinically relevant organisms or those that have been either in foods and outbreaks or in human situations. So he's evaluating doing the different plasmid profiling for virulence, antimicrobial resistance, et cetera.

These interactions now, as it gets into let's say pathogen displacement, that type of thing in the microbiome, that's a different aspect of the work.

DR. LEIN: Any questions or comments from the center representatives? Okay, so Donna and I have made the executive decision, we could take a 15 minute break. So we will see you back here in 15 minutes, which according to my calculations is 2:50.

(Break)

(Last session of meeting not transcribed due to problems with audio file.)