May 11-12, 2021: Science Advisory Board to the National Center for Toxicological Research Meeting Transcript

Please stand by for real-time captions.

I'm going to start recording the meeting now.

Audio recording for this meeting has begun.

All right, and looks look our captioner is in there. We look good there. Yup, the captioner is in. Our chair is there, Dr. Aschner. Board members, when we have a presentation and you have any questions during Q&A, please do me a favor and raise your hand because Dr. Aschner will be able to see that, and we can call upon you to then -- you can either unmute and speak orally or as a member, you can submit your question in the Q&A pod. You have a couple of different options there. Outside of that, Michael, you look great today.

Michael Kawczynski:
I will start kicking us off. Good morning, welcome to the National Center for Toxicological Research Science Advisory Board meeting. This is a two-day meeting. Let's get this started. I will hand it off to Dr. Aschner. Take it away.

Dr. Aschner:
Good morning everybody and to the participants, and presenters. Unfortunately, we can't be together in the meeting, but we have done it before. We have done it well, I think. So, the job attached is here, and we'll do our best to fulfill our mission again. I want to welcome everybody. As you know, the function of the scientific advisory board is to provide the NCTR with advice to look at innovative technologies, methods, developments, and the unique scientific expertise of the scientific advisory board, hopefully, can provide the director with some direction and helping and establishing, implementing, and evaluating the different research programs that ultimately assist the FDA commissioner in fulfilling regulatory responsibilities. We are basically an extra agency review panel. The function that we have to do is to ensure the research programs of the NCTR are scientifically sound and pertinent to the mission of the FDA. We have the long day and ½ and we will start today -- Donna is going to give us some information about different housekeeping items and then we'll hear a bit about the Center from Dr. Slikker. Last year, we reviewed the Division of Microbiology. The same thing is going to happen starting tomorrow afternoon, the Biochemical Toxicology Division is going to be reviewed. So we'll hear the report from the subcommittee that reviewed the Division of Microbiology, Dr. Kasper, and we'll present that. Then we'll have a break. We can work in a number of breaks. We'll hear the response and the division from Dr. Foley. We changed things from a few years ago. Rather than going directly into the different programs of the NCTR, what we're doing now is first we're getting the FDA center perspectives. We asked last year, the presenters trying to focus as much on how the centers interact with the

NCTR and provide us as much information on this part of their interaction. And we'll have a public session. I am not sure if we have any speakers today, but that is supposed to take place today between 2:00 and 3:00. And in the afternoon, we'll start hearing the reports or talks from the overview of the different research activities. We have three divisions scheduled for today, and we'll continue tomorrow with the other three divisions. After that the NCTR -- the SAB will meet in a closed session, we meet and formulate our opinions and have a closed session with Donna and Bill and Tucker. This is basically the agenda. I really don't have very much else to say. I want to thank Donna and Bill, all the presenters, and I want to thank all the board members. One thing that I want to mention, unfortunately, is that we lost not too long ago, Carl Cerniglia, the Director of the Microbiology Division. He was at the NCTR for over 40 years. I enjoyed interacting with him over the past years. He'll be missed and please keep him in your thoughts the next few days. What I would like to do next before we continue is to have each of the scientific advisory boards say a couple of words about themselves. I will start. My name is Michael Aschner. I'm at Albert Einstein College of Medicine and my interest is in neurotoxicology. If it's too cumbersome, we can skip this part. Donna, you let me know.

Dr. Mendrick: Okay, should be fine.

Dr. Aschner: Okay.

Why don't we get Charles? Go ahead.

Dr. Kasper: Hi, I'm Chuck Kasper from the University of Wisconsin at Madison, and I am in the Department of Bacteriology.

Dr. Aschner: Greg, please?

Dr. Lansa: I am Greg Lansa, Washington University Medical School, Department of Medicine, Cardiology. And my work is eclectic in clinical [inaudible] imaging and nanomedicine broadly.

Dr. Aschner: Ken?

Go ahead. Sorry.

M. Kawczynski: Ken doesn't have his audio connected at the moment.

Dr. Ashner: Okay. That is what I thought. Mary Ellen?

Dr. Cosenza: I am Mary Ellen Cosenza. I am a regulatory toxicologist and I specialize in biologics.

Dr. Aschner: I think Patty doesn't have her audio connected right there. I will go –

Dr. Ganey: Mickey, can you hear me?

Dr. Aschner: Yes, I can.

Dr. Ganey: Okay.

I know I don't see a little phone icon next to my name, but I did call in. I am Patty Ganey, I am Emeritus at Michigan State University as of February of this year. And I'm very interested in drug-induced liver injury.

Dr. Aschner: Okay. Thank you. We have.

Dr. Ramos: Mickey, I think I connected my audio.

Patrick?

M. Kawczynski: Sorry. Hold on a second. Who connected their audio?

Dr. Ramos: This is Ken.

Dr. Mendrick: Ken.

M. Kawczynski: Go ahead, Ken.

Dr. Ramos: All right, thank you. This is Ken Ramos from Texas A&M University and my area of interest is genomics.

Dr. Aschner: Somebody has both audio on the computer and their phones. So, if you're not speaking please mute yourself. The next one is Suzanne, please.

Dr. Mendrick: Are we just going to introduce the board members or have all of the speakers introduced?

Dr. Aschner: Just the Board, actually.

Dr. Mendrick: Okay.

Dr. Aschner: John Michael.

John Michael. Right. I left some people out. Okay.

Dr. Sauer: Hi, everybody. It's John Michael Sauer, I am from the Critical Path Institute. My interest is around drug development tools, specifically safety biomarkers. Great to hear everybody today.

Dr. Mendrick: I think that is it for the people that are on.

Dr. Aschner:
Okay. I don't see anyone else. Okay, so without further ado, I think I am going to, again, thank everybody and I think, Donna, you're next in the agenda.

Dr. Mendrick:
Yes. I need to read some legal material. I am the Designated Federal Official for the NCTR Science Advisory Board Meeting. We appreciate the time and diligent work of board members preparing for this meeting and

the forthcoming deliberations. I and the board wish to thank the FDA regulatory centers and NIHS to the participation in the meeting and all my NCTR colleagues for appearing in this meeting. Let me say a word about my role. As a Designated Federal Official, I serve as a liaison between the board and agency. I am responsible for ensuring all provisions of the Federal Advisory Committee Act are met regarding the operations of this meeting. Also, in my role, my critical responsibility is to work with appropriate agency officials to ensure that all appropriate ethics regulations are satisfied. Board members are briefed on the federal conflict of interest laws and each participant has filed a standard government financial disclosure report. We do have a full agenda, yet strive to ensure adequate time for the presentation, public comments, and board deliberations. The special note for all presenters, board and participants, please keep your video off and mute your phone until you speak. Announce your name. Be sure to turn off your video and mute your phone after you're finished. Pursuant, we have public commentaries scheduled for today. However, no one expressed an interest so we're going to continue with the meeting. The public comment period won't happen today. I would like to add during presenting and discussions, if board members require greater clarification from the attendees in the audience, they may request information from myself or the chair. The minutes will be prepared as well as transcript, both posted to the website. Please remember, this is a public meeting. I wish to thank the board for their participation in today's meeting. We did receive one letter from the Humane Society, which is posted on the Science Board website with other meeting materials. I will turn it back to Mickey.

Dr. Aschner:
Thank you, Donna. I heard you read the letter. I was thinking about this letter and I was not going to say anything about it. I thought about it and I am going to say something about the letter. One thing I would like to put on public record is that toxicologists are biomedical scientists and I will leave it at that. If you want to read it, go ahead and you will understand my comment. Okay. Without further ado, I will move to Bill. Dr. Slikker is director of the NCTR AND HE WILL GIVE US A HALF HOUR OVERVIEW OF THE STATE OF THE CENTER. BILL, PLEASE GO AHEAD.

Dr. Slikker:
THANK YOU, MICKEY. Welcome, everyone. It’s a pleasure to have a chance to talk about the NCTR and its accomplishments the last year. As importantly as that is, I also want to say, a thank you to the SAB board members. You are continuing a 30-plus year history of being able to assess the progress of NCTR and to help with your comments in improving its function and utility to the FDA. So, I really appreciate your efforts in doing this review. Also, of course, we have many members from other centers and operations within the FDA. That is really critical that they're here. Not only do we get to hear some of their needs and the collaborative studies we're doing together with them currently, but we get a chance to have them understand more about the progress at NCTR and how we can collaborate even more in the future. Also, I appreciate all of the presenters that have made their slides ready for today and tomorrow and are ready to present them. I appreciate that work. So, welcome to everybody, including those that are here to just learn more about the NCTR. We appreciate that very, very much. Let me go ahead and start with

the organization of the NCTR. A you can see here, we have many different groups within the NCTR. The bottom set of boxes, though, is where the research occurs. You will hear from each one of the divisions throughout the day and tomorrow. The management of this is really a very low percentage. Somewhere around 15 to 16% of resources goes in the management. So we definitely put the resources in the research divisions where they can get the most work done for FDA. We want to also mention our goals. Overall goals for NCTR and, really, what the NCTR does is advance the science, provides background and information for decision making for all of the different centers and offices within the FDA and helps devise new technology to do the same. And we do this through collaborations with the other centers and the offices throughout the FDA and this really does show that we're ever increasing the amount of interactions and collaborations we have. And finally, we also have a global outreach because of the status of our science and the roles that we play in leadership, not only nationally but internationally. We have a global presence to lead toxicology forward for the agency. This is really critical because the FDA relies on a lot of imports and those need to follow the same kinds of goals of being safe and effective and those produced within the country of the United States. It's important we bring along and interact closely with our global colleagues. I wanted to mention the science at NCTR. We have developed this through a number of partnerships, not only with the centers and offices of FDA, but with over a dozen academic institutions, other federal agencies -- which I will say more about later -- and a complete memorandum understanding with the State of Arkansas, one of the few between the FDA and state is right here and managed by the NCTR/FDA. We're proud about that interaction. That links us up with five major research universities, including a large clinical center and children's hospital within the state. Going through some of the opportunities we have for science at NCTR, of course, we look at the most modern and active areas of research doing technical improvements of those, understanding those, and figuring how to best use those for updated decision making. We certainly provide input to help the decision makers within the other centers have the data they need to make decisions, and we do this by really developing these tools and approaches in concert with the regulatory centers of FDA. We have also really addressed the COVID issue. I will be telling you more about that as we go through, but we do have over 15 projects that are ongoing in the COVID area. Such an important area right now for study. And with that, I want to give a diagram here. This changes from day-to-day because of new project beginning and ongoing projects being completed. Around 57% of our projects are in collaborations with others, mainly with the centers of the FDA, including CDER with 41% and others from 10 to 12 or higher percentage. This gives you a snapshot in time. It changes with over 200 projects and there are always those that are being completed and new ones started. We think this is critical. We appreciate the collaboration of what the other centers and agencies, etc. So, the expertise, though is key. You don't have expertise without quality scientists, which is what makes the difference here at NCTR -- the scientists behind these particular capabilities. Everything from bioimaging -- we'll say a few words with that later -- Inhalation Core and Nanotechnology Core. All of the different areas -- antimicrobial resistance, including virology, microphysicological systems, and certainly a lot in the area of neurotoxicology and virology. All these are important areas that are

improving to be applied to FDA decision-making approaches. That is why we're involved in those particular kinds of expertise, and we bring in scientists to study those, develop those, to devise experiments in those areas, and to publish in those areas. One of the critical features that we bring is this idea of bridging the toxicology paradigm. As we know, there is a lot of interest in emerging technologies: everything from bioimaging to various kinds of cell culture approaches, omics approaches, certainly, the idea of using chips as well as other kinds of MPS systems (Microphysiological systems). All of this is really exciting and important. The idea, though, is that how can we link it due to the guidelines studies that we have been using for making decisions for the last many years? So, one thing that NCTR can do because we have the capability of doing guideline-type studies is to compare and contrast the new emerging technologies against the established ones, making sure that these new technologies are going to be of utility to FDA for decision making. That is one of the areas where we have been moving into the last five or ten years. And this paradigm really means that we want to look across models, including humans, animals, cells and culture. It's really possible now, of course, to use human, nonhuman primate, rodent, mouse, et cetera, cells and culture and to compare those in many different ways, including understanding the pharmacokinetics exposure, which is really critical for modeling the outcome of these studies. Let's talk about COVID-19. I will talk about that through a variety of studies we're doing to let you know our progress. One of those areas that we have done in developing a new protocol just in the last year plus, plus executing those protocols has been a lot of progress in this area. One of those particular areas really is the idea of how you implement studies of COVID-19 and related viruses to work that can be useful to the FDA decision making. So we're really focusing on that particular area. Looking at biomarkers and tissue characterization, with a lot of emphasis on the immune system and on development, especially the idea of not only using the vaccines but various therapeutics to fight COVID-19, how do they interact with pregnancy and early life in the human population? One way to do this, sort of in a global way, is to look at wastewater. We have a project now where we're looking at wastewater and it's an opportunity to see how much COVID-19 viral end points are in there and compare those within communities. The idea is that you get an overview of what is going on within the whole community -- here we have three different sites within the State of Arkansas/Central Arkansas where we compare and contrast this by comparing to the clinical values and see if the wastewater evaluation will give us a heads-up on where the virus is striking and also, maybe new variants coming along. That is one project moving forward. Another focuses on the perinatal health risk assessment and this paradigm is really critical because now we've gotten approval to use the vaccine, at least one vaccine in children, in the mid-range -- we're talking about, in the 14, 15 area. That is critical. But what about moving to younger ages? We know the studies are ongoing, but they bring up a lot of points. What about the impact on the embryo and fetal development, early post-natal development? When do you give a vaccination to a pregnant mom where it will not only maximize the beneficial effects to the mom but also to the developing fetal system and to the newborn? These are all questions we can approach using this particular, in a perinatal system we have been developing. The idea here is that you're concerned about transfer. You're concerned about the effect on the

developing embryo fetal system, and you're concerned about its effects on post-natal development, etc. We have been able to move these studies forward in collaboration with our clinicians that we have collaborations with and with other portions of FDA. One thing that we want to emphasize is some of the technology to do this. A very exciting technology uses this idea of being able to use MALDI IMS and here we have preliminary data that actually can tell you about the mannos glycans track and how that relates to other indicators of immune response. You can start to really get an idea of the influence of COVID-19 and various other substances used in conjunction with treating the virus. You can get that information from the newer technologies. We're excited about these and we think they're going to guide us toward understanding more about the influence of COVID-19 kinds of effects on the immune system and the various agents used to treat it. One way is to think about the impact of this on the immune system. We have relationships with the University of Arkansas Medical Sciences campus and also, of course, within the Division of Systems Biology where we can analyze these samples, from the clinical sources, just to give us information about the influence of the compounds on the immune system. One of the exciting areas we have been working on now for eight or nine years is the human in vitro air way model. This allows to you look at human tissue in an in vitro setting and understand it's characterized fully, by the investigators within the Division of Genetic and Molecular Tox. It allows one also to compare and contrast to the outcome of the similar kinds of studies from in vivo approach. You can compare the technology that has been useful for many years against the newer technology, compare and contrast that, making sure the newer technology is giving you answers to be useful for FDA decision making. Using IPSCs is critical. And understanding more about the response of a group of humans, not just one human, but a group of humans -- how are we going to understand the variation in humans and as diversity in genetic background and the impact it has on the utility and effect of various drugs and chemicals the FDA regulate? This is another area where the interaction between the clinical lab, clinical sources and laboratories here at NCTR are very key. To go along with this, of course, over the last 10 or 15 years, the whole idea of the human microbiome has come into play and this is where the Division of Microbiology has been in the lead. Understanding about the system, the microbes that live on our bodies and in our bodies. Also, by adding individuals who know more about viruses, we have been able to develop this area of viral wholesale interactions. That has been critical to developing our approach to studying COVID-19 and the virus that produces that as well as mutants that are coming along that need to be evaluated as well. I tell you what is amazing is that this area has really been important for a whole host of reasons. One of those is looking at what is in the tattoos that now some 29-plus% of Americans have on their bodies. Are the tattoo solutions contaminated in some cases with microbiological contaminants? That is one study going on. Trying to understand more about how to keep Americans safe by understanding not only the microbiome, but bacterial infections in general. This is an area where this division has moved forward and another division I want to mention is the Bioinformatics and Biostatistics Division. There are many databases developed over the years that have been useful as bioinformatic tools. These databases can be useful for the reviewers to gather information more quickly so a lot of these tools have been placed on the desk of the reviewers within the

other centers and that makes their job more efficient to have access to the broad amount of data. To give an example of that, there is one called the FDALabel that's been historic for us and interactions with CDER and CBER have been profitable in this area. A recent survey showed that there are many different individuals that use it within CDER, some 200 CDER uses per month. And out of that, we had 67 responders with over 88% satisfied with the tool response. This shows that not only we're developing software that can be useful, but it's being appreciated by the reviewers who use the tools on a daily basis, oftentimes. Other areas that this division is pushing forward is the whole thing about artificial intelligence and machine learning. This is around for many years. The idea of applying it to pharmacology, toxicology, and safety assessment is something that is gaining a lot of momentum. So, certainly, this division is the heart of that movement here at NCTR and within the FDA. It can be used for food safety and for a variety of drug studies. This is all something that we're doing in conjunction with the other centers of FDA. And it shows also that we give consults, oftentimes, we'll have reviewers that ask our scientists to give them our responses and give them consults to various kinds of packages that are going through the FDA. You can see here both for NDA and IND there are many different consults provided. This is just the ones to Office of New Drugs within CDER, we have done this for other centers as well. Another indicator, a marker of how we're doing and it indicates that there has been a lot of use of these consults, probably averaging six or seven per year for just the one office as I demonstrated here. So, the idea is using this artificial intelligence power to look at drug repositioning and this has been so key, of course, during COVID-19 kinds of affects where we're looking at mainly agents that have been repositioned to provide protection against or treat the symptoms of COVID-19. And certainly, this particular approach always out in front with new technology with moving things forward already two manuscripts in preparation. The idea is to look at a variety of different agents that are out there and select artificial intelligence approaches, the ones that are successful and evaluate them. Make that knowledge known to many within FDA. This project's moving forward nicely, one of the many COVID-19-type projects that we have.

Let me switch gears for a second. I mentioned something about the Division of Neurotoxicology. One of those areas of interest is the developmental exposure to heavy metals. We heard a lot about arsenic in recent years but there are others as well that fit into the category. We have been looking at this in conjunction with the partners at CFSAN who have responsibility for baby food, cereals, as well as many other foodstuffs. What are the developmental effects of arsenic in the rat and other models like zebrafish? These are studies moving forward with different groups and some of them being funded by the Perinatal Health Center of Excellence, other ones in coordination with CFSAN or CVM. So, we're happy with the way this is progressing. There will be more studies to come in this important area in the future. Another area that the Division of Neurotox is looking into and has progress on is the idea of brain-on-a-chip. And here, we're talking about the possibility of having neurons, astrocytes, endothelial cells and neurons and compare them not only to between animal models but up to the human situation. And so – one can start to evaluate this whole idea and you will hear more about this from our Division of Neurotoxicology to culture these things under

parallel physiological conditions to compare and contrast. You know, the idea here is to move this area forward and not only can we do the on-chip approach, but we can compare that to whole animal responses as well. That is where you can get your added value out of that kind of comparison. It's one way to look at biomarker of neurotoxicity is to use imaging. We have fantastic in vivo imaging capability, including two MRI machines, a small board/large board machine, also a PET, again, a large board/small board machine which also can look at CT at the same time and compare to the PET. These are available. These approaches allow you to do lifetime study or recovery, insult and recovery. Protect of the nervous system and that is applied to both cancer studies and cardiovascular studies as well.

One area that is really unique to the NCTR is the Nanocore facility. This is a group activity between NCTR ORA with a lot of support from NIHS and NTP as well. This approach that has been available new the last 10 years or so is a state-of-the-art laboratory that has all the equipment necessary to evaluate, identify, and characterize various kinds of nanomaterials and to develop standards. This is a key part of this program as it moves forward, the development and acceptance of standards. This is all been written up in a recent publication that looks at nanotechnology over the last decade, and Anil Patri, the FDA chair of the Task Force of Nanotechnology, who is also the manager of our Nanocore is one of the people behind this work that has come out recently, summarizing the great progress that has been made across many government agencies and the FDA as well.

So, let me finish up by talking about strategic plans. This is the area we're looking at in the last year or two. One, of course is to prepare for the next pandemic and I will give you some input on that. Mainly not only to develop the new strategies, protocols and data, but also look at the facility. The other area is -- looking at this area of rare diseases. This is focused on developmental effects and the use of various agents to treat developmental rare diseases using artificial intelligence and other approaches to accomplish this. This is another area we're looking at investing heavily in the future. The access of corporation and technology. We have been talking about that the last few minutes. The idea is that you can't do that, unless you also compare them to the accepted guidelines studies of today and make sure new technologies are going to be affirmed and useful for FDA decision making. So these two go hand-in-hand -- the idea of developing and exercising the emerging technologies and confirming them against guideline studies to make sure they are going to be useful for FDA.

I just want to finish up by saying there is a lot of activity going on and interest in the Biosafety Lab 3 Level situation. We have some of the labs that allow to you look at the various viruses. We have some of those within the FDA, but really, not too many that can do animal studies as well as in vitro study, so we're interested in developing that capability here on the Jefferson Lab Campus to be available to all of FDA and we'll provide the opportunity to do level three work for the FDA. What we're finding is that when we wanted to start level 3 studies, that lab space was really difficult to find. We tried both within the FDA and we tried outside of the FDA. Of course, there is a lot of competition when some

studies need to be done, as they have been needed during the COVID-19 outbreak. To have the facilities valuable will allow us to get the work done quickly on behalf of the FDA and allow other investigators from all the FDA offices and centers to use the space. And that is one thing we're pointing toward in the future. This is a long-term goal that would take three-plus years to accomplish. I think it would be a tremendous edition to FDA's capability for fighting viruses and other like issues in the future.

Another area I mention side the rare disease area. We're putting together grant and support work for this. There is some work ongoing but more needs to be done. Really, what we're hoping is that all the centers will see some benefit from this idea of rare diseases and how we can approach them. Especially those that affect development and where we can certainly apply the latest artificial intelligence and other kinds of modern approaches.

I want to spend a couple of minutes on the agreement between the NIEHS and the FDA. This has been a very important agreement with a history of over 25 years of work and allowed the NCTR to strengthen the knowledge within the FDA for both the NTP and NIEHS as well. The idea is that we work together in a collaborative sense by inviting in the ideas and thoughts from the various centers, blending them with resources and support from NIEHS and the FDA and using that to get the work done. So, it's resulted in much work over the years that has been useful to FDA decision making. And the way it basically works, it's part of the National Toxicology Program, which has NIEHS through CDC/NIOSH and FDA/NCTR is sort of the coordinator for this. Goncalo is the FDA liaison to the NTP and helps coordinate the offices and centers to get the most out of this particular arrangement. This is where the NTP is now. It's evolving because we have new leadership within NIEHS. We will be moving forward with new agreements in the future and want to keep the strong relationship and ability to generate data for FDA decision-making available to us. Just to give you an idea of what we were able to do in the past, you can see important compounds that have been evaluated under this agreement -- anything from DEHP and phthalates with CDER and CBER, of course, the whole idea of the effects of gaseous anesthetics on development, primarily with CDER, the standards development that I mentioned within the nanoscale area, also AZT and many other like drugs looked have been looked at, Brominated Vegetable Oil with CFSAN -- a lot of work is done that is critical and we would love to see more of the work done in the future. So FDA can make good decisions based on that solid data. Not only are we reaching out, of course, for support from across the agency and other sources, but we also look inward and say, okay, how can we work on the availability of the funds to do research? We call them discretionary funds. Really, what do you buy the test tubes with? What do you pay your post docs with? What do you buy your animals with? What do you buy your cells and culture with? How do you do your clinical connections. That is what actually drives the research and those funds are critical to getting research done. How can you maximize those? One thing, we're looking at our payroll and NCTR contracts to see if there is a way too maximize that to retain as much as possible to get the research done. We're looking at different ways to reduce the stabilized cost in general. We're also looking for recommendations from our own

leaders here at NCTR and other centers and to find ways to reduce cost. The whole idea is to really implement cost savings where we make more money available for getting the actual research done. And in conjunction with looking for a new source of revenue or enhancing revenue, we're looking at ways to save money so we can make more money available for research.

Let me finish up by looking at our special programs. The FDA Perinatal Health Center of Excellence has been in existence for three-plus years. It's been a positive influence on getting support and data generated on this important period of time, including the maternal pregnancy period, premature infants, the neonatal period and through childhood development. It's a broad definition of perinatal health but the idea here is to focus attention in that area. Why is this beneficial? This virtual center allows us to garner resources to support research across the entire agency and we can look at things like maternal/fetal pairs, how this is a unique set, how one influences the other and how you can start to understand the sole transfer of drug effects from the fetus, et cetera. And also the idea of looking at preterm and neonatal individuals from the animal model point of view and human point of view. This helps us, then, address the issues by working with teams within the FDA where there's a lot of attention on perinatal health the last 10 or 15 years. To give you an example, we fund studies. This funding is determined by representatives from each one of the centers and some offices within the FDA. Each center has a chance to have their influence felt. You can see the lead of these studies varies from the various centers that are here: CBER, CDER, CFSAN, CVM, and NCTR all have recently benefited from support and highly collaborative. You can see all the collaboration going on with these other centers including CVM, CFSAN, CDER, CBER, and NCTR. These are the projects moving forward. This particular approach has been very useful to us in moving progress forward in this area of perinatal health.

A final close with advancing our global mission and global regulatory science research through a group coalition of ten countries and the EU and this has been very successful. We're now in our 10th year of doing this. Here are some of the past meetings – 2018 was on dietary supplements held in China and we try to move the meeting around to various parts of the world and our partners in this. 2019 was on nanotechnology and nanoplastics and was done in northern Italy, and the one that just concluded in September was our tenth anniversary one on emerging technologies and application for regulatory science. A great success here with over 50 different presentations. We really appreciate everyone's input into this and there is an overview manuscript that is coming to submission here soon.

Let me finish by saying that we will have the 11th Global Summit, which will be focused on this whole idea on artificial intelligence. The regulatory science for food and drug safety, real world data and artificial intelligence. We have some great opening comments coming from our Acting Commissioner, Janet Woodcock, and from the Deputy Commissioner of Food Policy and Response, Frank Llanos, the Director General of the Joint Research Center in Europe within the EU and that is Stephen Quest. We'll have speakers from four, five, six different countries. We're

looking forward to this. It's a virtual meeting, from October 4th through 6th.

Let me close by recognizing our scientists. I think another metric you have to consider is the impact and leadership that our scientists at NCTR have provided over the years. An example of this, if you can look at 20 of our individuals that have been very productive, you can see the numbers of manuscripts ranking up to four-hundred-sixty-something for our senior scientists. But numbers are one thing – another thing that I think is an even better metric is the impact of that. You can see here the number of citations from individuals, these top seven or eight individuals having an average of somewhere around 12 to 14,000 citations and going up every day. This is quite amazing and is an indication that the work is appreciated, the reference is cited because it's quality work and is making a difference in the leadership of science throughout the world. I am proud of our researchers and they are the face of everything that NCTR does. With that, I will close, and I don't know if I have time for questions, but we can always have those during the break or during the meeting. Thank you very much for your attention.

Dr. Aschner: Thank you, Bill. That is a lot of exciting things at NCTR. I think we have time for questions. I will open the floor for members of the science advisory board. Does anyone have a question?

Reporter: To ask a question, raise your hand to be called upon or unmute yourself to be able to assist. To raise your hand is at the top of the screen.

Dr. Aschner: I will ask a question, Bill. These are different times. How flexible and nimble is the NCTR? Has there been any need to shift resources from one division to another, for example, to carry out COVID-19 studies or pretty much everyone keeps going on as they did before, the beginning of 2020?

Dr. Slikker: As you probably know, Mickey, from your own research area and knowing other colleagues as well, COVID had a tremendous impact on, I think, research across the U.S. and the world. Certainly, that was true at NCTR. With over, you know, 18 new projects on the COVID area, and new ones being brought up almost every day, it's been a tremendous impact for us in terms of emphasis. I mentioned a few of those along the way. I will hear more about them throughout the day and tomorrow. But, it has meant that we started new projects in COVID and have data coming out now from just a year ago or the last time we met. This has been really amazing. The other sort of index for this is that many of these projects have been funded by competitive funding mechanisms. And this has been really important to us because the Office of the Chief Scientist and Office of the Commissioner have made funds available and we have been very competitive getting some of the funds within a few months after the COVID issue hit. And more since then. So it's not only a matter of getting together and getting the work done, but also we have been able to attract funding to get this work completed.

Thank you.

Are there any other questions?

Dr. Ganey: This is Patty. I have a quick question. So, Bill, [Inaudible] [echo] I am wondering if you are agreed to -- what you currently have or are you building another whole facility for that?

Dr. Slikker:
Right, you know. This is very critical. And the reason it is is that it takes really a quality facility. Everything from the air handling to the actual laboratory setting, including animal rooms in this case. So, this has to be a new facility. So, what we're looking for are these NEF funds we call them. They're funds sometimes made available from Congress with funds that are leftover from previous years. We're really hopeful we can attract that kind of funding and that is why we're talking about a 2 1/2, three-year project to actually build a new building that would have all of these capabilities that you need. There is no reason to go into this halfway. You have to go in 100% and means you have to hire new technology and new people. We have individuals that have this training. We have a great safety group here. We'll have to add to that to make sure we have all of the ducks lined up to make this happen. It's a heavy investment, but it's one where it would give the FDA the capability of dealing with the next pandemic. We know that those incidents occur every three, four years, at least that is how it's been the last 15 or so, and, therefore, we need to be ready for the next one. This one will allow us to be ready for that.

Dr. Aschner: Thank you, Bill. Any other questions? I don't think so. Let's move on. Thanks again, Bill.

Dr. Slikker: Thank you.

Dr. Aschner:
I guess our next speaker is going to be Dr. Charles Kaspar. We'll hear the report from the scientific advisory committee on the review of the Division of Microbiology. Go ahead, Charles.

Dr. Kasper:
Okay, thank you, Mickey. Good morning, everyone. This presentation will highlight the findings of the subcommittee's review of the Division of Microbiology at NCTR. I will use the following outline for the presentation that includes the members of the subcommittee, acknowledgments, the mission and areas of emphasis, and finish on future goals and summary. Subcommittee members included Dr. Suresh Pillai, Professor of Microbiology and Texas AgriLife research fellow at Texas A&M University. Dr. Douglas Rhoads, Professor of Biological Sciences and Program Director for Cell and Molecular Biology at the University of Arkansas. Dr. Mary Ellen Cosenza, who is the co-chair of this committee and President of MEC Regulatory & Toxicology Consulting, and myself, Chuck Kaspar. I am Professor of Bacteriology at the University of Wisconsin-Madison. The subcommittee would like to acknowledge and thank the following individuals: Dr. William Slikker, Dr. Donna Mendrick, Kimberly Campbell, Dr. Carl Cerniglia, Dr. Steven Foley and all of the scientists who made oral and poster presentations last year. The

subcommittee would also like to acknowledge the loss of the division and longtime director, Dr. Carl Cerniglia. I am sure this will be a tremendous loss. Carl was part of the NCTR/FDA for more than 40 years and received a number of FDA awards. Please let the members of the subcommittee know how we can support NCTR and the division during this period of transition.

The mission of the Division of Microbiology is to serve a multipurpose function with specialized expertise to perform fundamental and applied research in microbiology in areas of FDA's responsibility in toxicology and regulatory science. Areas of emphasis include evaluating the impact of antimicrobial agents, food contaminants, food additives, nanomaterials and FDA-regulated products on the microbiome. Developing methods to detect and characterize microbial contaminants in FDA-regulated products. Determining antimicrobial resistance and mechanisms of food boring and other pathogens. Conducting research to aid FDA in the areas of women's health, tobacco products and nanotechnology. Finally, improving risk assessments of FDA-regulated products. The division divided and presented projects into three topic areas. Which the subcommittee then evaluated. Those topic areas include food safety and virology, microbiome and biological interactions, and microbial contaminants detection. General comments on the Division of Microbiology as a whole, the division has a total staff of 39, comprised of 27 FTEs and 12 ORISE positions. Of the 27 FTEs comprised of 19 scientists and staff fellows, four support staff and four administrative staff. This division is productive and contributing to FDA's mission. On average, they produce or publish 25 to 30 publications per year with some results used to develop regulatory guidance. It's evident that collaborations with NCTR divisions takes place and outreach activities at the national and global level have kept research relevant and up to date. An example of this is the launch of the virology group, which provided support on the pandemic.

Over all observations and suggestions: The subcommittee recognizes the importance of communication with other divisions at NCTR and centers within the FDA and encourage division staff to continue and expand these interactions. The subcommittee acknowledges the personnel changes made since the last review. And there is some concern that the division's resources are spread across too many projects and in some cases, may not be connected to core areas of emphasis. It's important for the division to prioritize its core areas of expertise, what areas of research provide the most value to the agencies while remaining true to the mission of the division. What are the top three core competencies in the division? And what is the proper mix of support staff and scientists? Looking forward, there is a need for an active hiring and succession plan. It's estimated that 42% of the scientists within the division will be eligible for retirement the next five years.

The first topic area we'll cover is food safety and virology. This is an area of high priority. There is evidence of interactions with other FDA centers. Projects within the topic area include antibiotic-coated medical devices, updating DNA sequence databases and bioinformatic tools to identify important genes, rapid development for pathogens and FDA-regulated products and more recently, virology. These projects represent large multidisciplinary areas in microbiology or any one of these

particular areas or projects could easily involve all of the division staff. An example of this would be in bioinformatics and virology. What are the strengths of staff working in food safety and virology and how many of the approximately 40 staff work on each of these projects? Its delicate balance between emerging topics and core strength. Specific comments related to projects within the topic area, adding virology was forward-thinking. This was prior to the pandemic that took place. An experimental model of spike protein inflammation are valuable and supported by NCTR capabilities. Salmonella virulence and plasmid databases. This work is significant since predicting them to be valuable during regulatory science, epidemiological investigations, risk assessments and the identification of pre-harvest risk factors. It's important that the projects utilize NCTR expertise, including multidimensional tissue culture and the animal facilities to confirm gene functions are predicted by the bioinformatic approaches. Lastly, within this topic area, methods for salmonella detection in spices. The work is noteworthy because the developed method will be added to the Bacteriological Analytical Manual or BAM. There are many unknowns on pathogens or pathogens in the transmission by low-moisture foods, particularly spices. This particular project utilizes multiple areas of strength within the Division of Microbiology.

Microbiome and biological interactions. Overall comments for this particular topic area. This is an area of priority. There is evidence of interactions with other FDA centers. The approach examines the impact of xenobiotics and nanoscale materials on the human microbiota, which is a reasonable approach. The projects include examination of the FDA-regulated products of the microbiota of the intestinal tract, vagina, and skin. A shortcoming of this approach is changes in microbiome need to be linked with established toxicity or health markers such as immune disfunction or DNA damage. This will take time and resources and it's possible there is no link between the microbiota and some of the other established human health markers.

Specific projects within the topic area include the impacts of xenobiotics on intestinal tract microbiota. Changes were observed and unclear if they're significant. Nanoparticles in vaginal products. Good progress has been made on this particular project, particularly with vaginal epithelial cells. There is a need for linkage between changes observed in the mouse vaginal microbiota and the human vagina. The next projects nanoparticles in sunscreen products. Interesting findings in this particular project, but there was concern the experimental approach doesn't adequately simulate the surface conditions of human skin. Lastly, the toxicity of nanocrystal drug formation on intestinal epithelial permeability and immunotoxicity. Strong collaborations with centers with interesting results were observed or presented with this particular project, but it was unclear how this fits within the Division of Microbiology.

The last topic area is the detect of microbial contaminants. Overall comments for this topic area. This is a high prior area to the FDA. There is evidence of interactions with other FDA centers. Our projects investigating microbial contaminants in tattoo inks, pharmaceutical products and fecal transplant specimens. The subcommittee suggested

conducting conventional culture and culture-independent methods in parallel. Additionally, sequencing can provide additional information about contaminants. Specific projects within the area include the survey of tattoo inks. This is relevant work hampered by a limited number of samples from suppliers, at least at the point in time this data was presented. The project would benefit from the use of culture and nonculture methods for the detection of contaminates. The second project was fate and detection from burkolderia and pharmaceutical products. This is important work, particularly as relates to the development of the oligotrophic medium. There is value in conducting culture and nonculture methods in parallel. Further exploration of the genetic basis of long-term survival may provide insight for control of contaminants. The last project present side the standardization of sporicidal efficacy assessments. This is a focused project and of importance to food and pharmaceutical industries. It might be possible and beneficial to partner with other federal laboratories to understand the spore formation, persistence, and inactivation.

Last year, there was a poster session. These were short presentations and summaries presented online. These were very well-done with summaries of key findings presented in a clear and concise manner. The topics the committee found of particular importance to the FDA, mission included. The induction of virulence genes by antibiotic-impregnated catheters, UPEC mutations and fluoroquinolone resistance, fecal transplant specimen characterization and storage, culture of human intestinal microbiota for fecal transplantation and factors influencing plasmid transfer in bacteria.

Finally, summary and future directions. Also some questions. NCTR's Microbiology Division is contributing to FDA's mission on a variety of topics. This division has done a decent job in attracting and retaining staff. The microbiology division is communication and collaborating with other division at NCTR and FDA centers, encouraging involvement with appropriate FDA working groups. We encourage division staff to have regular formal and informal meetings to promote intra-NCTR communication and interaction due to their spread across the NCTR facilities, in different buildings and locations on the campus. They must build bridges with universities to identify and attract staff. The challenge for the division, probably for all of the divisions at NCTR, is to identify core strengths and balance with an ever-expanding list of challenges, technologies, and emerging issues. It will be difficult to make significant progress. The subcommittee is not saying progress hasn't been made, but to use one of Bill’s words to “maximize” progress on emerging issues and even the current array of projects with the existing staff, there must be a prioritization. And the identification of core strengths made. The division can consider partnerships with croups at NCTR, FDA centers, universities, and private sector to get necessary support for high-demand expertise such as in bioinformatics. With that, I want to thank the administration for all their help in the production of this review and all the scientists and presenters during last year's meetings. I would invite other members of the subcommittees to clarify any points or add to what I have already presented.

Dr. Aschner:
Thank you, Charles. Okay, I will open the floor now does. Anyone from the subcommittee or in general from the Science Advisory Board have any questions at this point? [Inaudible]

We can hear you, but it's -- I don't know how to describe it. It's with an echo.

Dr. Cosenza: I'm on the phone. Okay.

Dr. Aschner: It's better now.

Dr. Cosenza:
Okay, I wanted to add my thanks to the presenters on the microbiology group. It was a very collaborative discussion that we had also amongst my fellow subcommittee members and in preparing this report and feedback. I, too, want to add my condolences about the unexpected and sad loss of Carl. I am looking forward to the feedback from Dr. Foley. I looked to the slides ahead and I know it's going to be a collaborative discussion. I think some of the feedback, particularly on the last slide, applies to other areas not just to the microbiology area, in terms of the collaboration within the NCTR, outreach to universities. One thing we didn't talk a lot about, but I think we should be thinking about is how do we develop a pipeline as toxicologists? It's difficult to hire them, but we tend to focus on the acute hiring and the need right now. We should also be thinking about the long-term pipeline and how do we educate scientists for the future.

Dr. Aschner:
Thank you, Mary Ellen. Any other comments? If not, I want to thank the subcommittee. I think you have done a very thorough job. I am sure Bill will appreciate the recommendations that you have. I would like to ask the Science Advisory Board next. We have to vote on this report. I hope everybody had a chance to read it. We have several options. Accept it as written, changes, or to reject it. If you look on the right-hand side at the bottom.

M. Kawczynski:
I will pull it in, Michael. I will pull it in on screen. As a reminder, only, and I repeat, only the science board members are allowed to vote. No others are allowed to. If you're not a science bord member, don't click on any of the voting options. At this time, science board members, if you look below Dr. Aschner, have three options. Accept as written, accept with changes or reject. We'll give you about a minute here to submit your vote.

Dr. Aschner: We should have nine, I believe, right?

M. Kawczynski:
Yup. Do not close whoever -- let me run the vote. All right, so far, we have seven that are in there.

Dr. Aschner: Eight.

M. Kawczynski: I want to double-check and give more time before.

I want to double-check and give more time before we have 9. I will double-check. All right, I am going to end the poll. We're going to broadcast the results. Accept as written as unanimous.

Dr. Aschner: Okay. Thank you, Michael.

M. Kawczynski: No problem.

Dr. Aschner: And Donna, I defer to you. We're scheduled for a break right now. I don't know if you want to take a break, come back at 11:00 or whether we should head back to Foley, and do the response and -- Foley, get the response and take the break as scheduled at 11:00.

Dr. Mendrick: Whichever you prefer?

Dr. Slikker: Hey, Mickey --

Dr. Aschner: Yeah.

Dr. Slikker:
Do we have a moment? I think we're ahead of schedule. That I could respond, I think it was Mary Ellen's suggestion about training. I would like to take a minute or two to respond to that. I think it's a critical question.

Dr. Aschner: Go ahead.

Dr. Slikker:
The idea is that there are trainings going on at every level within the NCTR. We have, of course, our postdoctoral program where we support trainees for three to four years. That program usually has in it anywhere from, you know, 40 to 60 individuals. Those individuals already have their Ph.D. and they are getting their postdoctoral training within the NCTR laboratories. Oftentimes, they collaborate in projects with others. Therefore, many stay within the FDA because they are well-trained and respected scientists, and they don't have opportunities as some within the NCTR but, but many more within the other centers of the FDA. That is a positive thing for training at that level. For training individuals during the Ph.D. period, we have that opportunity as well. I have had the privilege of training 12 Ph.Ds over the years. Many other individuals out here have also had the opportunity to be consult to the trainee and to be their major professor, if you will, by having adjunct components at university systems. There has been much Ph.D. work accomplished here at NCTR over the years. Actually, you know, probably close to 100 of these individuals. Maybe more. And then, for the undergraduate, we also have a summer undergraduate program, which Paige McKenzie and Laura Schnackenberg run now. We've had this program for over 20 years. Each summer, we train 20 to 30 individual undergraduates for a 10-month organized course and they worked with mentors within the various divisions to pick up skills and to keep them interested in the sciences. So, this is another area where we do this. In addition to that, a lot of scientists work with students during high school to help them with

science fair projects and to keep them interested and grow interest within the sciences. Yes, we agree with you, Mary Ellen, that this is important, but I wanted to numerate some of the many things that the NCTR staff does to really keep that pipeline full. We certainly participate in all of the scientific societies to work with students there, too, by signing up to have individual interactions, one-on-one kinds of things, interviews with students and, of course, to attract more of them to come to work for FDA and NCTR in many cases. Appreciate that sentiment. We know it's important and we're doing what we can. If you have ideas how to do more, please let us know. Thank you.

Dr. Aschner:
Thank you, Bill. Okay, I suggest that we go on, actually. Let's have the response from Dr. Foley. It's 45 minutes, so, if you finish in 45 minutes, we'll be back on time. We'll save time later in the afternoon. So, Dr. Foley please go ahead with the response to the subcommittee review.

Dr. Foley:
All right, can you hear me okay? All right.

Dr. Aschner: Yes.

Dr. Foley:
Wait for the slide deck to come up. All right. I'm here to give the reply to the response to the SAB subcommittee report. Initially, Carl was scheduled to give this, so I, considering we have the disclaimer, this is not a formal dissemination of the FDA and does not represent agency position or policy -- like I said, this this is Dr. Cerniglia was initially scheduled to give this presentation. About a month ago, we unexpectedly lost Carl. It's been kind of a big challenge for the division both from a professional standpoint and a personal standpoint as well, too. Carl's been here at NCTR for over 40 years with the founding director of the Division of Microbiology. The only Division Director. There he was recently awarded the FDA lifetime achievement award, which is given annually to -- Michael, I think we can hear you talking or typing. And, you know, so he was given the lifetime achievement award for FDA. Given the one scientist each year a distinguished alumnus of North Carolina State University, you know, and even had a bacterium named after him. You know, for us, he was a strong mentor. For each of us in the division and so he's going to be greatly missed. You know, the untimely nature of his passing is evident that he was the one who prepared the presentation and everything that I am about to give. Hopefully I can give him an honor through this presentation. First, we all want to reach out and say thank you to the subcommittee that was there for the review. Dr. Kaspar, thank you for the nice overview that you gave about the division review. Thank you for serving as chair. Dr. Cosenza, the co-chair and Dr. Pillai and Dr. Rhoads, too, who served on the committee as well. We appreciate the thorough review, the comments, and the discussion we had during the review that occurred in August. You know, we're currently working on trying to work through the report and address some of the issues that were brought up in there.

The focus of the subcommittee review was, again, the Division of Microbiology and addressing also the quality of our science, research productivity, strengths and opportunities that are out there and the relevance and integration of the division's research into the FDA mission and NCTR mission, public health as well too. The committee did a nice job, and Dr. Kaspar alluded to some of these in his presentation, about the research going on and providing information on, or suggestions on methodological approaches in those types of things in there to help our science in the areas of food safety, antimicrobial resistance, nanotechnology in the cells, virology, and the microbiome research within the division. With the meetings, it was a day of, 2 1/2 days. One in the afternoon where we focused on the three topics, food safety and virology topic area. Each of the four, each of the tree topic areas had a larger presentation in them. Dr. Kasper eluded, we had the poster session, too, which allowed each of our division PIs to present their research and so the poster session here is listed under food safety and virology. Not all of the posters fell into that. Some were on contaminants and some on microbiome as well. This happened to be placed here in the schedule. I want to acknowledge our division principle investigators and support staff as well, too. They did a great job in their presenting as during the subcommittee review. They are doing a lot of good research and trying to help promote the FDA mission and public health as well. Some of the broad things or positive input that we appreciated from the subcommittee was that the Microbiology Division focal areas are relevant and directly applicable to the FDA mission of product safety. So we're trying to do work that helps the agency and benefits public health, too. Dr. Kaspar alluded to this, the poster session that we had and that where we did have a number of short summaries and online posters for the subcommittee to review and a variety of topics, including antimicrobial resistance, fecal microbial transplant, in vitro models, that sort of stuff. The subcommittee, Dr. Kaspar alluded to, felt that they were well-done with summaries of key findings. I appreciate the nice comments on the poster session. As we look at some of the details of the subcommittee report and some of the overarching things related to the microbiology program, we agreed with the subcommittee that our research expertise lies in areas like antimicrobial resistance, host-microbiome interacts, environmental biotechnology, nanotechnology, virology and salmonella virulence. The subcommittee highlighted our efforts, collaborating across our center here at NCTR with each of the different divisions as well as the Nanocore and veterinary services. This is something we're happy about, to have these interactions with other parts of the center because it's important to move forward. One of the concerns is being spread too thin, and I think the ability to work across different divisions will help strengthen some of those without spreading us too thin in some areas. Related to national and international outreach, different collaborations, I think the subcommittee, Dr. Cerniglia and his initial comments in the subcommittee review talked a lot about our communications with the different groups, either internationally-nationally within the FDA and within the center. You know, and we'll talk about that more tomorrow in the division overview as well, too. And I think the committee those collaborations kept our scientists up to date, kept our science relevant and highlighted this, especially related to how we were able to ramp up fairly quickly our virology group to help provide critical support and research during the COVID pandemic. Now that reaches beyond our division

as well, too where Dr. Acevedo and her team served as a research across the centers as well, too, for the different groups that are trying to tackle some of the issues with the pandemic. Related to research productivity, we appreciate the comments that subcommittee that we have a strong publication record, where we have approximately 25 to 30 publications each year. These include peer-reviewed publications, book chapters, you know, symposium and workshop proceedings. They don't capture some of the work we do providing data to the regulatory centers to help with some of their regulatory decisions. Sometimes they don't necessarily show up as a peer-reviewed publication, at least initiation, but they do provide data that can help drive the regulatory decisions in there. Going forward, we want to continue or ramp up, if we can, the publication stream. Looking at publishing, continuing to publish in high-impact journals and research focus areas. Then, continuing to drive data that will help with the FDA's regulatory science mission. Related to communications and recruitment, this has been alluded to a couple of times that there are challenges with trying to recruit, especially post docs and junior staff to central Arkansas to NCTR and within the Division of Microbiology. One of the things in the review that we talked about was our interactions with the universities. But, quite rightly pointed out, most of the interactions are with Arkansas Universities due to geography and types of things. We have interactions with UAMS, U of A Fayetteville, U of A Pine Bluff and Little Rock. The committee felt we needed to expand that pool and start to develop our interactions with universities outside of the borders of Arkansas. We concur with that. It will be valuable to do that and we're starting to do that. We have some concepts and other things where we're reaching out to universities in different states and different areas too. Which should help to provide the linkages to increase our applicant pools for post-docs. Another thing that was brought up was to utilize looking at, going to conferences and national meeting placement services at conferences to allow us to identify potential candidates and interview those. As we exit out of the pandemic over the next year, this can be something we do in person, where we reach out and identify potential candidates from our interactions with the different universities and let the meetings introduce those. A good way to identify candidates and bring them in. We appreciate, again, with communication and recruitment. We appreciated the comments from the subcommittee that we're filling a national need and that we have within the division, again, we have been able to attract significant talent and we want to continue to do that in there. We also want to continue to open up our communication channels with the other centers as well as within the NCTR. One of the things we have discussed and both in the division and NCTR as well, too, is having quarterly research presentations or seminars to the different product centers to describe our research and capabilities that we have here. As well as having periodic seminars with other FDA stakeholders as well, too, maybe on the less structured basis or whatever. We've got interest, there is joint interest from different workgroups and that stuff that we're on. Having those types of interactions to identify priorities and to avoid being overextended to those things as well. This is something we're going to continue to look at and try to figure out the best ways to do that. One of the things the pandemic allowed us to, or showed us, there are good resources on the computer and that stuff, to facilitate good interactions. Kind of like what we're doing now with the SAB review. That being said, we do realize,

especially with recruitment, there are challenges for the division and the Center as well, too, trying to recruit talent and support staff to help our programs grow and have the scientific capacity to address emerging issues as they come up. Some of the challenges that we've got are due to financial constraints and facility spaces and one of the things that we don't really want to do is to bring in new staff that is very talented and that kind of stuff and then not have the resources for them to being successful. We're trying to be proactive as we work on recruiting efforts as well, too. This is going to be key as Dr. Kaspar pointed out. We do have a fair number of scientists that are retirement-eligible the next five years. Trying to figure out the ways to -- that is going to be important. You know, some of the ways that we are going to do that is, again, reaching out to our FDA center colleagues to identify emerging areas where they feel that there is needs, reaching out to university contacts to let them know when we have open positions, looking at the job placement boards within the American Society for Microbiology and those types of things, too, to be able to attract the top talent that will fit in to some of our core research areas as well, too. One of the things we talked about was the need for increased bioinformatic support. If you look through some of the comments during the subcommittee review and the comments in the document, saying this is not just an NCTR or Division Microbiology-related issue, this is the university's struggle with this as well, too. We have great tools to generate large volumes of data with sequencing or proteomics, those types of things in the bottlenecks analyzing and interpreting that data. You want to take a multipronged approach with us. The key one is to work with our Division of Bioinformatics and Biostatistics to help in these efforts but also, working to develop some internal expertise in that area, if you're training. Other opportunities to developing computing resources to allow us to have some success in this area. It's going to be important as well and as we recruit new principle investigators and those things, too, that might be something we want to look at or assess as we look at the candidates for different positions. Looking toward the future, as a subcommittee, we want to mention the importance of our interactions with the different FDA working groups. We want to continue to do that and enhance that where possible so that we can have a good pulse of important issues within the agency. We already have a number of scientists working in -- on work groups in food safety area of the microbiome, antimicrobial resistance, nano, and to continue and maintain those and if there are areas to expand and with our more junior activity is to get them involved, too and to help with a development of research. It's important. We're working to try to identify our core strengths and build up core strengths so that we don't have the overextension. Again, I think that is not just a microbiology issue, but I think that is one of those where we need to look at our core and strength, look at the facilities and equipment and that kind of stuff that we have, address the challenges that we can do the best job. If there are areas where we are not the best well-equipped, to not jump into those and because it's not possible for us to cover everything that the FDA needs with the existing number of staff and space. I appreciate the comment that Dr. Kasper made, that in one of those different areas, there might be, the whole staff could address one of those areas, which is true. I think we have some core areas that we want to build out and address. As we look at the thoughts on the different topic areas that we presented on and the subcommittee

provided comments on, in the food safety and virology area, we appreciate the positive feedback. The subcommittee felt we were satisfying agency needs in multiple areas, including the microbial methods, salmonella, pathogen and microbial resistance. We really appreciated the comments about our communication with the different centers and collaborating, you know, and working in a collaborative area with the different centers. I appreciated the minute about the virology section. I think Dr. Acevedo and her group has done a great job in being a resource and helping with responding to this pandemic and her recruitment and addition of virology expertise was the result of a previous subcommittee recommendation to do that, and so, we take the comments and recommendations to heart. We will continue to do that with the information that we have got from this one as well, too. On the virology side of things the subcommittee noted it was exciting that our division and NCTR is playing a strong role in the COVID-related pandemic response which is shown by the ongoing projects in the division. Dr. Slikker alluded to some of those during his overview and we will talk a little about that tomorrow in our division presentation, too. Dr. Acevedo and her team are playing a key role. One thing we were able to do is in this response, we've got multiple investigators that have different expertise. So, Dr. Acevedo has a background in Coronavirus research. We have had investigators like Dr. Bruce Ericson, a strong molecular biologist who was able to be pulled in to work on the cloning and that sort of stuff. We have Dr. Wagner, Drs. Khare and Gokulan who have a strong expertise in the host side of the microbe-host interaction, and they were able to be brought in to address some of those issues on some of the research that we have going on. So, we were able to flexibly develop teams to tackle them. That was one of the things, which is good. It allows for -- we have good communication amongst our division and people willing to work together as a team to address the complex issues. I am happy, proud of the work that the teams have done there. On some of our work related to salmonella, virulence and plasma, we have two presentations. One by Dr. Han and Dr. Khajanchy talking about our work, our collaboration with Center for Veterinary Medicine—both the Office of Research and Office of New Animal Drugs & Evaluation. The committee, I think, appreciated the work that was done there. One of the things, a lot of that work has been on the in vitro and silico side. I think there is an interest to expand that out to look at the pre- and post-market production practices, the different factors that may influence the transfer of plasma-securing genes associated with the pathogenicity or antimicrobial resistance as well and we concur. That is a good recommendation. We're working with our Center of Veterinary Medicine colleagues to try to move that forward as well. Another thing related to the efforts was to take the in vitro and in silico efforts and move them into the animal models. Dr. Khajanchy has a concept that was recently approved where we were planning to collaborate with a university outside of Arkansas to try to move this into animal studies. Again, this likely be in collaboration with the Center for Veterinary Medicine and CFSAN colleagues as well, and on the virulence and database project, the subcommittee recognize it's a valuable tool and that will be useful for the regulatory communities for things like recalls, epidemiological investigations, risk assessments, and pre-harvest efforts. This work is being done not only in collaboration with others within the FDA, but also, we have working in an interagency fashion with USDA, CDC, and NIH on some of this. The goal is to move some of the virulence pieces into

the NCBI sequence analysis pipeline, too, to have the resources as people generate sequences to get some potential prediction of virulence or at least identification of a different virulence factor on the plasma. Dr. Kan talked about -- had a nice presentation on his work with salmonella and spices. And this work was a collaborative project in CFSAN and this has been moved into the BAM as Dr. Kasper mentioned. Some of the things the subcommittee suggested with spices is to broaden that out to also look at enteric viruses and protozoa that may be contaminating spices. WE think that's a good idea. This might be one of those areas where we don't want to expand to areas, where we don't have prime expertise at the moment, but CFSAN does, for example, has experts in enteric viruses that are right now tied up in COVID-related stuff like Dr. Acevedo is here and they have experts in protozoa. These may be good potential to be able to work together on these spices. Switching to the topic two, the microbiome and biologic interactions, you know. One of the things the subcommittee said was that we have got a reasonable approach to assess the impacts of the materials. However, we need to expand that and try to look at a link between the changes of the microbiome and establish human toxicity markers. Then alternatively, looking at, do some of the exposures and changes in the microbiome lead to an increase in susceptibility to infections? Neither do the altered flora and in there moving that and looking at that in animal models. The microbiome, we're working with a variety of different centers across the agency and with other division within the NCTR as well, too, so try to tie in the microbiome into some of the toxicity assessments and those types of stuff. So, our scientists here do concur with the comments in trying to move these findings into more of the human results, the human toxicity, that kind of stuff in there, so, we look at the individual projects here. Dr. Khare talked about their work on xenobiotic interacts with the gastrointestinal tract. And this work is being funded through the National Toxicology Program, looking at a difference number or compounds like arsenic, BPA, triclosan, silver, trying to understand the impact on both the microbiome and microflora as well as the immune response. The host immune response during the peri- and post-natal exposure periods. These efforts are using a variety of different in vitro and in vivo models, trying to develop initial work on understanding the best routes of exposure. And then they're also using both non-animal models as well as ex vivo host intestinal tissue, getting them from the different bio-banks and the impact there as well. The initial findings from the studies have provided information on the microbiome and the host immune status. As we go forward in these areas, the next stages are to try to understand are the changes we see, quote, unquote, good or bad? You know, using the following approaches, we'll try to understand the susceptibility to infection and metabolic diseases, the long-term effects of short-term exposure, single exposures, and how long does that last trying to understand the correlation between developmental toxicity and GI toxicity and understanding the importance, the relevance of the animal models for susceptibility to disease. As these studies are continuing to progress, the data that is being generated, we feel that the research results are helping to generate data that is important or will assist the different regulatory agencies and making decisions on safety and evaluating the toxicity of compounds. One of the things our scientists here are--they're interacting a lot with scientists across the center and they will continue to do that and try to share our microbiome expertise as well

with the different investigators across NCTR. Dr. Chen talked about their work with nanomaterials associated with sunscreens and the impact on the skin microbiome. We appreciated the feedback in there and one of the concerns was the, it was a lot of the work was done with a single organisms that are part of the skin microbiome and, I think the committee felt it was important to look at maybe a bit more realistic exposure approaches, having a complex microbiota, maybe trying to do more with bringing in the skin portion as well, too, and our investigators here appreciate that. As we're going forward and developing this, this work that is something that we're going to integrate as well. Dr. Gokulan talked about their efforts on nanocrystal drugs and interacting with CDER. The subcommittee in the report had not a lot of comments on this project in there, but they felt that we were getting some good data from this, important data and interesting findings. Then continue to move that into some of the animal models as well, too, to understand the difference between the nano formulations and the parental formulations of different drugs. Dr. Wagner talked about the office dilemmas health project, looking at the safety evaluation of nanoparticles that might be incorporated into feminine hygiene products. The subcommittee felt that those two provide nice results. However, I think a lot of the work has been done with the mirroring vaginal model. The subcommittee felt there was a need to take that and see how those results translate to the human vaginal model. Something that would be considered as we go into the future. Right now, Dr. Wagner is just ramping up a COVID-related project as well as wrapping this one up. So, I think as we look forward to next steps on these Office of Women's Health-type projects will be to take these suggestions and move them forward. Topic number three was the microbial contaminants detection. Some of the overarching comments we had here, that the subcommittee felt this was an important area where we were making good results for the agency in a number of different products. We work with CFSAN, CDER, CBER on some of the different efforts. One of the things that was a concern was that we're relying a lot on conventional culture-based methods and some of the basic sequencing methods to characterize the different pathogens that might be present in these different products or detecting the pathogens. There is a belief we need to advance in the sequencing approaches and we agree. We have concepts in the pipeline that will take the projects to the next steps to incorporate the next-generation sequencing. One reason why we had not had a lot of that was our initial studies were based on some of the FDA guidance documents and some of the approaches and USP guidelines and stuff for the culture, sort of serving as the gold standard for those. We do agree with that suggestion and are undertaking efforts with some of the concepts that have been recently submitted and are going through the approval process to do that. We do agree with the feedback that we're working well with the other centers in collaborating on a number of projects. We have good communication, regular communication with our partners in the contaminants area. Especially with the Burkholderia work, where we're working with CDER on this. *Burkholderia cepacia* contamination is a big problem for pharmaceutical products because it can lead to opportunistic sections and a lot of, if there is contamination in the drugs that go into immunocompromised individuals, that is a huge, huge issue. So, we need to have sensitive methods to detect pathogens and so, Dr. Han and his team have done quite a bit of work with developing media to help with the resuscitation and growth of these, but also, moving into and

utilizing flow cytometry. As well as molecular genetics sequence approaches as well to augment the culture-based methods. Had some recent publications in this area. So, to develop rapid and sensitive diagnostic methods to detect the pathogens and in the pharmaceutical products and that this, these efforts are continuing again to build in more of the next generation sequencing approaches. On tattoo ink, this was mentioned earlier as well, too. We're doing quite a bit of work with the CFSAN office of cosmetics and colors. Here, we have done multiple surveys of tattoo ink, permanent makeup, and microblading inks. In our initial assessment, we found a fairly high number, a high percentage of tattoo products that were contaminated with different bacterial species, including some that might be opportunistic pathogens. We have been -- had subsequent investigations working with CFSAN closely on this to look at a number of some additional products as well as longitudinal like samplings of inks. Right now, we have efforts that are just getting underway and looking at detecting anaerobic bacteria. The other work was primarily with aerobic culture and methods. We want to look at that bacteria as well. The committee, I think, felt this work was appropriate for the FDA research. Dr. Slikker mentioned 29% of adults have tattoos in the United States. This is an important issue if there is contamination and leading to soft tissue infections. We appreciate the nice comments from the subcommittee. Other products, another projects is on the developing standardized methods for sporicidal efficacy assessment and developing optimized spore preparations methods. You know, spores can be a large problem -- recalcitrans are often difficult to inactivate and so developing methods to detect the spores and to assess whether sporicidal products are working efficaciously is important. So the subcommittee felt like this was a needed research area and from the food and pharmaceutical industries, they tell us -- I think -- with that, related to that, it's not just an FDA issue, I think, but it goes across the Federal Government. We should be reach outing to federal laboratories, too, to work on these challenging issues as well. That is something we're doing. We're working to reach out and make the bridges to help push this research forward. All right, some of the overarching recommendations the subcommittee had was there is a need to focus on prioritizing research and emphasize those that are likely to provide the best benefit to the FDA mission. That is something that we're looking at. We're trying to determine, okay, what are our strengths? Where can we provide the best bang for the buck, if you will, for the FDA? Part of that is through working to enhance the communications channels with colleagues from the FDA centers and the NCTR as well, too, so that we can come together and be a large team to answer complex questions. We have right now, our balance, within the division as we have a high percentage of research scientists relative to the numbers of support scientists and so we're trying to assess is what is the proper balance there? Do we need to have a more balanced ratio of research scientists, the support scientists? Having division support scientists may help with some of the flexibility issues as well, so we're trying to develop long-term staffing plans. One of the things that we have been doing, in doing, that we need to take into account we have a fairly high percentage of our investigators who are retirement eligible. Dr. Kasper mentioned the number 42% and in the next five years. So we need the balance the recruiting of research scientists as well as the support scientists so we maintain that scientific base with research scientists but also as people retire, also,

increasing the percentage of support scientists who facilitate research being done. Again, somewhat tied to other things. We want to make sure we carefully balance our ongoing research. The expertise we got with the emerging priorities, I think, by defining our core areas of strength, this will help us do that. It will also help to identify individual strengths within the division where we don't necessarily all have to be experts in everything or we can work together where we have our expertise and reach out to others in the division or across the center to help with that so we can address some of the complex challenging public health issues. Again, we have -- we're trying to be proactive in our hiring with the microbiologists and post-docs and support staff in there. I think the suggestions are reaching out to universities across the country is a great one to do that. And develop those pipelines to bring in talented staff. Again, encouraging the communication, regular meetings, that is a good suggestion as well, too. The way the division is set up is while we do have labs and offices and different areas, we do have a core group of offices which helps with some of the communication. With the pandemic and having a lot of people working remotely hasn’t benefited that a lot, but as we're getting more fully in-person, we have good opportunities to discuss our research. I think we will continue to do that, having formal meetings as well as some of these informal communications to look at ways to optimize our expertise. I think we do have core expertise in a number of areas: host-microbiome interactions, salmonella virulence, virology, nanotechnology, women’s health and environmental biotechnology. One of the things we want to do as we look at strategically is can we augment these? Can we help to build these up? And identify within these maybe, what are our core strengths in these areas? [Captioners transitioning]