National Center for Toxicological Research (NCTR)

Meeting of:

Science Advisory Board (SAB)

April 4, 2023

FDA

(Virtual Meeting)

Proceedings by:

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P R O C E E D I N G S (9:00 a.m.)

Agenda Item: Call to Order and Welcome

DR. GANEY: Welcome, everyone. Thank you for attending this meeting. In a moment, I'm going to ask for introductions, but I thought I should start by reminding the SAB board members what our role is. We've been charged to provide independent scientific guidance, technical advice, and recommendations on strategic direction and mission relevance, as well as perceived strengths in areas of growth. In particular, we're asked to look to the future and help NCTR to discern what might be coming trends and where they should be headed.

I would also like to remind each of us, when we're not speaking, to stay on mute, and when we are, to unmute ourselves. We've all done that.

Finally, it's your choice whether you have your video on or not, but as we go around and introduce ourselves, I might ask that you turn your video on for at least that point in time. So I am going to go around my screen and ask you to introduce yourselves.

On my upper left is Dr. Patterson.

DR. PATTERSON: Thank you, Patti. Tucker Patterson, I'm the center director at NCTR.

DR. COSENZA: Hi, everybody. I'm Mary Ellen Cosenza. I'm a board certified regulatory toxicologist,

currently consulting and adjunct at University of Southern California.

DR. KASPAR: Hi, my name is Chuck Kaspar. I'm a professor at the University of Wisconsin in Madison.

DR. RAMOS: Good morning, everybody. I'm Ken Ramos from Texas A&M University in Houston.

DR. TROPSHA: Good morning. I'm Alex Tropsha. I'm a professor at the UNC Eshelman School of Pharmacy, Computational Chemistry and Computational Toxicology.

DR. SAUER: Hello, everyone. John-Michael Sauer, I'm currently vice president of Nonclinical bio. I'm also an adjunct professor at the University of Arizona.

DR. TONG: I am Weida Tong, deputy director for the Division of Bioinformatics and Biostatistics of NCTR.

DR. WALKER: Good morning. Cheryl Walker, I direct the Center for Precision Environmental Health at Baylor College of Medicine in Houston.

DR. GAMBOA: Good morning, everyone. My name is Goncalo Gamboa da Costa. I am the senior science advisor at the Office of the Center Director and also the FDA liaison officer to the National Toxicology Program.

DR. BELAND: I am Fred Beland. I am the director of the Division of Biochemical Toxicology at NCTR.

DR. MENDRICK: Good morning. I am Donna Mendrick. I'm the associate director of regulatory

activities at NCTR. I'm also the designated federal official or DFO for this meeting.

DR. GANEY: Thank you. Great. All your tiles get moved around, so I'm going to miss some people. Dr. Lanza?

DR. LANZA: Good morning. I am Gregory Lanza, Washington University Medical School. I'm a professor and cardiologist.

DR. PATRI: Good morning, everyone. My name is Anil Patri. I'm from the National Center for Toxicological Research, Nanocore.

DR. FOLEY: Thank you. Dr. Steve Foley, director of the Division of Microbiology at NCTR.

DR. VAN BEMMEL: Good morning, I'm Dana Van Bemmel. I'm with the FDA Center for Tobacco Products.

DR. VALERIO: Hi, good morning. My name is Luis Valerio. I'm with the Center for Tobacco Products, associate director in the division of nonclinical science.

DR. FITZPATRICK: Suzy Fitzpatrick from the Center of Food Safety and Applied Nutrition.

DR. CAMACHO: I am Louisa Camacho, deputy director for the Division of Biochemical Toxicology at NCTR.

DR. SCHNACKENBERG: Hi, I'm Laura Schnackenberg. I'm the division director for the Division of Systems Biology at NCTR.

DR. EPPIHIMER: I am Mike Eppihimer. I'm the division director of biology, chemistry, and material sciences in CDRH.

DR. GANEY: I guess, John, you need to figure out why we can't hear you when you unmute yourself.

DR. HEFLICH: Hello, I'm Bob Heflich. I'm the director of the Division of Genetic and Molecular Toxicology at NCTR.

DR. GANEY: Thank you. I am Patti Ganey. I am professor emeritus from Michigan State University. As Donna mentioned, I am sitting in for Miki for this meeting as chair. Donna, I'll turn it back to you for conflict of interest.

Agenda Item: Conflict of Interest Statement and "Housekeeping Items"

DR. MENDRICK: Thank you. So as I said, I am Donna Mendrick. I'm the DFO for this meeting. I'd like to welcome everyone to our Science Advisory Board meeting. We appreciate the time and diligent work of our board members in preparing for this meeting and for their forthcoming deliberations. I and the board wish to thank the FDA regulatory centers for their participation in this meeting and my NCTR colleagues for all of their efforts.

Let me say a word about my role. 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, regarding the operations of this board. Also in my role, a 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 in the provisions of the federal conflict of interest laws. In addition, each SAB member 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 the board's deliberations. A special note for all presenters, board members, and other participants, please keep your video off and mute your phone until you speak. Announce your name when you do so since this meeting is being recorded and a transcript will be posted to our website. Be sure to turn off your video and mute your phone when you're finished.

During presentation and discussion, if a board member requires greater clarification on an issue requiring participation of attendees in the audience, they may request this information during the meeting through the chair or myself.

You will notice that pursuant to FACA, we have scheduled a one-hour public session this afternoon to

revise comments being considered before the board. We've gotten requests from the Physicians Committee for Responsible Medicine to speak for five minutes. On our website you will see we have posted documents and slides as well as from the Humane Society of the United States.

In accordance with FACA, minutes of this meeting will be prepared, as well as a transcript. This meeting is being recorded and all will be posted on the website. So again, I will just thank the board in participation of this meeting, and thank you, Patti, for acting as chair.

DR. GANEY: You are welcome, and thank you for those reminders.

Tucker, would you like to give us the state of the center?

Agenda Item: State of the Center

DR. PATTERSON: Sure, Patti. As I'm pulling my slides up to start, I do want to thank everyone for attending today. As most of our board members are aware, we suffered a very catastrophic tornado on Friday that came through the Little Rock Metro area. So some of our staff lost property, some severely damaged property, and others are still dealing with power outages. So just thank everyone for their perseverance during this time and know that our heartfelt sympathy goes out to our staff who have suffered these losses and we certainly want to assist in

any way that we can. So as the word keeps coming in on folks, we're going to try to make a concerted effort to respond with assistance once we gather all of the information there.

So I want to start out with really just a high level overview. I appreciate our board members. Most are definitely familiar with NCTR, are not rookies on the board. I'm going to make this very high level. Also, I don't want to steal any of the research thunder from our division directors, but I do want to point out some of our ongoing and future projects that we're going to be pursuing as we move through this presentation.

So of course I have to put the disclaimer up here that these are my views and any mention of products or for clarification, are not intended as an endorsement or recommendation.

So, many of you have seen our mission that we want to address the needs of the agency. We want to serve as a global resource for collaboration training and innovative scientist solutions. I think you'll see that as we move through the presentation. We want to provide reliable data for FDA's decision-making. This is becoming more and more critical as the agency of course has been in the spotlight in the past few years with a number of issues, not to mention the COVID-19 pandemic, and we want

to develop innovative tools to assist the FDA in this decision-making, and we will support, of course, the FDA's public health mission.

So we are a unique resource. We celebrated our 50th anniversary a couple years ago. It's hard to believe that was that long ago. We do have five offices and six research divisions, approximately 500 employees. I'll get into more detail on that in a few minutes.

We are solely owned and operated by the agency. We don't lease our space. We have a little more flexibility with how we can modify here and I'll show you some of the modifications that we have incorporated the last couple of years, over a million square feet of offices, lab space, 30 buildings, over 100 labs, and we recently received our renewal for our AAALAC accreditation.

Some of our recent renovations, I know several of you have not been out to the property since pre-pandemic, but we have a newly renovated Building 14 lab space and we have labs from our DGMT division. Also, biochem tox, DSB, our chemistry group, which is under the Office of Scientific Coordination, also has laboratories in that building.

We've upgraded our sidewalks, culverts, parking lot lighting, which is nice. One of the things that many folks have complained about, really since the

implementation of cell phones, is our limited reception here at the facility, but now we have a distributed antenna system that helps us in all of our offices, laboratories, across campus, and so we have adequate cell phone service now throughout campus, even down in the lower bowels of some of these buildings we can get cell reception now.

We're getting ready to begin some renovation in our Building 62 that will now have multispecies housing. We have some new pathology labs that hopefully will start within the next fiscal year, and then also a data recovery center that's slated for FY24 to be built here at the facility.

Our organizational structure, many of you have seen this, we're focusing really today on the bottom tier, our six research divisions. You'll hear from our division directors over the next two days, and then we'll have the subcommittee review of our division of systems biology that's now headed by Dr. Laura Schmackenberg.

As far as our personnel, I incorporated this year our contract staff because they are a very critical part of what we do here. So we have a little over 500 staff when you include our contracts. The first four blocks or so are the scientific, what I call, our really boots on the ground folks. When you get into our administrative staff there, that's a little bit misleading with the number, because

that also includes a lot of our support staff within the Office of Scientific Coordination.

It includes our safety security staff, our Scientific Computing Branch which is under our Division of Bioinformatics and Biostatistics as well as our Office of Management, Office of Research, and Office of the Director. So that's why that number looks a little heavy, but a lot of that I consider direct research support and not what we consider true admin, budget analysts, and management staff.

You can see our contract staff there. That's our animal care, our maintenance, we have an on-site pathology contract, our security, our custodians, our cafeteria make up the bulk of that.

So I do want to point out that out of our approximately, I think we have around 230 active what I would call research projects, the majority of those projects are indeed collaborative in nature. When I say collaborative, I mean we have collaborators from different entities that are on those projects. This is not solely just a funding aspect, but this is our collaborations, other scientists that we're working with, and you can see that the majority are from CDER. Most of our projects are CDER-centric, but we do encompass some projects that are

really across the agency and I'm going to show you that in a little bit more detail in the later slides.

When you look at other federal entities, we have many groups that are represented there, CDC, NCATS, NIEHS, of course with our NTP, NCI, and others as well.

I want to focus your attention here to the first and the third column, but just historically, over the last five years and really during the heart of the pandemic here, you can see that our manuscript output still maintained around that 150 per year average in our peer-reviewed publications, and our new protocols that were coming out around 50 per year. Our technical reports as we're closing out these projects and so typically what we like to see is those technical reports equaling the new protocols, and as we're developing new protocols, we're closing out old protocols, not only with manuscripts, but with final reports.

So I'm going to move into some of the ongoing studies here that we have with the product centers, with our sister centers and also with other agencies. You can see as I move through this next set of slides that we do work really across the divisions to support our colleagues at CDER.

When I say DNT, that's Division of Neuro Tox, and Division of Biochemical Tox, Division of Bioinformatics and

Biostatistics, and also our Office of Scientific Coordination which oversees our FDA label database.

You see supporting CDER there. The Zika virus work actually was funded through the medical countermeasures and that's headed up by Dr. Dayton Petibone in our Division of Genetic and Molecular Toxicology. Then of course we have some work there in our Division of Systems Biology as well.

I do want to mention this of course is not all-encompassing with these projects. This is just a snapshot of some of the projects I wanted to highlight. We support CDRH; of course, extractable, leachable chemicals from medical devices is an issue that they want to address. So our Division of Bioinformatics and Biostatistics are working on that, division of microbiology and antimicrobial resistance and bio film marker. I'm going to get into some more detail later about some of our AMR work.

And supporting CFSAN with nano materials with our Division of Microbiology and also pharmacokinetics of cannabidiol in our Division of Biochemical Toxicology.

Supporting CVM, we have alternative assessment approaches for toxicity of veterinary drugs and bioactive substances, also in DSB, and looking at virulence mechanisms of avian pathogenic E. coli in DM. We also support ORA through tattoo-related skin infection research

that we're doing in the Division of Microbiology and also the C. bot bioassay in regulatory food samples. Our Office of Scientific Coordination really is our vet services group, supporting our sister center here at ORA which houses the Arkansas laboratory on our campus. So they don't have their own vivarium so we support that C. bot bioassay.

Supporting the Office of Minority Health and Health Equity, we have a project looking at racial disparities that's in our Division of Bioinformatics and Biostatistics. We also have a project looking at the Native American community and that's getting a lot of traction right now. We have an office within the agency, of course, that looks at Native Americans and the health disparities within that population, so we're supporting that.

Also, the Office of Women's Health, we were very successful this past year. I believe we had five of our six projects that went forward for internal funding to the Office of Women's Health that were funded. So DSB and DBB both have projects within the Office of Women's Health that are ongoing.

The Office of the Commissioner, we're looking at a certificate of analysis of cannabis-derived products. We also are supporting CTP with this ENDS delivery system

using air-liquid interface, or ALI, model. Also, DBB is assisting them as well with this ASSIST4Tobacco database.

I do want to mention the National Toxicology Program, because they have been an integral part of what we have done here at NCTR since 1979. We still are part of that triad along with NIEHS and NIOSH. Dr. Goncalo Gamboa da Costa and myself, we have sat in on many, many meetings over the last three years or so. The focus has changed with that, but we are still very much involved in the NTP and also have published many papers over the last 40-plus years through the work that's done through the NTP.

So some of the examples here that we have ongoing are within our Division of Genetic and Molecular Toxicology. You can see with sex-specific variability, with o-phthalaldehyde, using alternative models, also looking at the role the microbiome plays in xenobiotics and also the characterization of nanoscale materials within our nanocore. I'm sure Dr. Patri will be discussing that in a little more detail later.

So I want to change directions here and talk about the predictive tox roadmap because a lot of our work is really migrating to support PTR. You can see here 41 percent of our active NCTR protocols right now are under the predictive tox roadmap. We have BA funds, our budget authority funds, are earmarked for work in this area, and I

want to expand on that, but you can see the focus there is the toolset is needed to enable sound comparison of value limitations of these currently accepted testing paradigms and new methodologies and approaches under consideration. So I'm going to try to expand on that in the next few slides. Currently, we have about 95 fully approved protocols that are PTR applicable. Each research division at NCTR has anywhere from 10 to 20 protocols that focus on PTR.

So what do we want to do under this PTR, under this predictive tox roadmap? Of course, we want to explore these new alternative methodologies. We're focused on the three Rs. We want to identify rare toxicities, we're looking at low-dose mixtures. Mixtures of course are a serious issue, not only for us but with other agencies as well, such as EPA, and we want to enable streamlined processes in public health emergencies. So really, our rapid response toolkit that we're working on developing.

So at NCTR, we want to test these models and the assay reliability, address these data gaps, potential non-genotoxic carcinogens, we want to characterize those, look at chemical transport, brain, across the fetal barriers, and also we want to develop computational tools which you'll see probably expounded on greatly by Dr. Tong as he presents their work at DBB. But of course, a lot of work

in the artificial intelligence and the qualitative structure activity relationship area.

So with our ongoing PTR studies this year, you can see that we're doing the PK study for inhalation of nicotine and DBT. We're using Alzheimer's on a chip modeling and neuro-tox AI methods for food safety and DBB.

Also, looking at biomarkers of safety, efficacy, of genetically modified Leishmania parasites as vaccine candidates, and this work is being done in our Division of Systems Biology in collaboration with our colleagues at CBER.

I want to try not to steal too much of Weida's thunder here, but I do want to talk about our ongoing development and maintenance of our regulatory bioinformatics tools. If you had the chance to attend SOT a couple of weeks ago, you know that this is a huge area right now of consideration for the agency. How do we implement, how do we adopt some of these tools in the regulatory framework? So this is really just a laundry list of some of the areas that we're addressing, a lot of database development. Again, you'll see this in more detail later.

Also, FDALabel, we had a computer set up at our booth, an exhibit booth at SOT, and Dr. Hong Fang who oversees this initiative, she's in the Office of Scientific

Coordination, people could come by and they could see how the system worked, and she could train them on doing some searches.

You can see the MAQC project, many of you are familiar with that. It's been going on since around 2006, still moving forward now, moving into the sequencing quality control, so a series of really high quality manuscripts have been published in this area. Of course, continuing to refine our LTKB database and look at DILIrank and also our DILIst dataset.

I just wanted to point out how popular this has become. Dr. Fang has done an excellent job with the training. I think in FY23 they've seen over 700 participants so far that have been trained across the agency. She did a remarkable job, her, and her staff, of rolling that training out and continuing to update FDALabel. It's becoming a very popular, hopefully, resource there that our product centers can utilize.

I'm not going to get into a lot of detail on this one because I know you'll see this slide again, but you can just see that this AI4TOX, this AI program is really developed to advance FDA's toxicological research and it consists of these four initiatives. You can see the animalGAN, the SafetAI, the BERTox, and the PathologAI which is a preclinical digital pathology with artificial

intelligence, and I'm sure we will get into more detail later.

So I really want to finish up with talking about where we're headed. You've seen where we are right now, where we've been, but where we want to move our research at NCTR, you'll see this as our division directors present their work and where their individual divisions are heading, but these are our high-level focal areas right now at NCTR, and I want to just briefly touch on each one of these as we move through the next set of slides.

So with artificial intelligence, you can see that this work is done within DBB, but we are implementing this across our research divisions and you can see that enhancing the IND review process, computational modeling, to address AMR, which is in collaboration with our colleagues here in microbiology. More AI methods for food safety, virtual animal models to simulate animal study without actually using animals within that study, and looking at AI natural language processing in current labeling documents.

When we talk about implementing new alternative models, that's part of the PTR and moving forward. So we're still charged with conducting this holistic assessment of what these toxicological liabilities and products are that we regulate, and we all know that it's

not as simple as dropping something in a cell culture and then having all of your questions answered. We know that we're still dealing with complex interplay of tissues and organ systems.

One of the pushes to implement NAMs is the high cost and time required to perform animal testing, and that is indeed true. Animal experiments are extremely costly and they can be labor intensive. But we also have to realize, too, that we aren't quite there yet on the organs on a chip, the tissues on a chip. They're great screening tools and you'll see as I move through these slides that we have implemented many of these at NCTR in looking at the three Rs, but right now, we've estimated that you're probably looking at about 80 different platforms to recapitulate one rat. So we're just not quite there yet, but we are moving in that direction.

So you can see some of our NAMs that we've implemented. We have a 3D spheroids model. We're looking at microfluidic systems there in DSB. Liver chips for drug-induced liver injury, Dr. Qiang Shi in DSB has done a lot of work in this area, and we've got some new projects that aren't yet approved that we're moving forward also within the Division of Systems Biology.

Of course, cannabis, CBD, it's in the news, it's an issue. We have several projects that we're moving

forward in that area, from immune-modulating effects of perinatal CBD because we know that there is in-utero exposure here, looking at these combinations, we have a project with methadone or buprenorphine looking at neural stem cells, looking at the PK of CBD because we know that it is different depending on which species that you're utilizing, and also looking at a CNS activity and toxicokinetic bridging study within DSB.

I did mention before the AMR. Most of this work is through our Division of Microbiology which is headed up by Dr. Steve Foley. You can see the virulence mechanisms of avian pathogenic E. coli and also the nanoparticle work that they're doing, working on xenobiotics in the GIT, and also the role of plasmid factors in virulence and also antimicrobial resistance.

Opioids, still an issue, we all know that that probably only increased during the pandemic. When you're talking about money that's earmarked, there is BA money that's earmarked for opioid research. So we're mandated to do opioid work and opioid work only with that money that's been earmarked. So you can see that Dr. Hong in DBB has a project there with this OAK knowledgebase. We're looking at sex differences. There seems to be an issue with abuse potential between males and females. Looking at the molecular metabolic effects of chronic opioid exposure on

kidney tumors and their microenvironment, that's a project that's under review. Also, looking at developmental neuro-tox, that's another project that's under review that we hope to move forward very soon.

Perinatal health and pediatric internal medicine has really been a focus of NCTR's work really since I've been at the center, which is the early 1990s. You can see that we have several projects in this area across all of our research divisions. We have the CAR-T project, that's Dr. Mercer in DSB. We have the project in DGMT as well. We have the montelukast project that's under review, that's Dr. Slavov in DSB. So really, the whole gamut here of perinatal health, pediatric internal medicine, and I'll get into some of our PHCE projects in a few minutes.

Rare disease has really come to the forefront recently and we were fortunate to be able to participate in FDA's Rare Disease Day that happened in February. Dr. Jess Hawes, who is the deputy director in the Division of Systems Biology, gave an excellent presentation from NCTR, highlighting our work that we're doing in this area, which you can see that we have other divisions as well that are working in the rare disease area.

Really, it's come more to the forefront over the past few years. We know that there's a population out there that really is just not represented very well in our

drug development, because for the financial gain with these drug companies, they don't really want to pursue that, they want to pursue these drugs that 50 percent of the population is taking and not that's targeting a very low percentage of our population. So this is really a needed area to address.

Minority and women's health, that's another area that needs to be addressed. We have a lot of projects across all of our research divisions. You can see that we have a virtual pregnant woman modeling suite that we are developing and trying to move into that direction. Early signs of sex difference in adverse drug effects of course is really needed. New alternative models of folliculogenesis for assessing drug and chemical toxicity, that's within DSB.

You can see in-vitro permeation testing to investigate the role of race and ethnicity and skin pigmentation on the permeation of cosmetic ingredients, now that there's been some realignment within the agency, I think if anything, probably our work in that cosmetic area is going to increase.

Our Rapid Response Program, we already have some projects that do provide a rapid response. We want to continue to develop this with these emerging outbreaks that happen, that the agency has asked to quickly address.

These are some of the projects that we have ongoing right now that we can really stop what we're doing and address this C. bot toxin bioassay which is along with our colleagues at ORA at our Arkansas Laboratory. We have norovirus infection and norovirus salmonella coinfection. We're looking at establishing an in-vitro model for that.

SpecID, Dr. Dan Buzatu with the Division of Systems Biology has the capability to look at not only pathogen detection, but also this is both viruses and bacteria as well as chemical detection. Then we have this whole-genome sequencing vibrio project in the Division of Microbiology.

So I want to finish up with just discussing our Perinatal Health Center of Excellence. This was established in 2018 to really target projects within the agency and provide funding across the centers within the FDA. It's not just that we're strictly NCTR, but we actually manage the financial aspect of the program here at NCTR, but you can see the criteria here that the PI must be at FDA.

We also have an annual meeting in October. Our 2023 annual meeting is going to be in October. Once a year, all of our PIs come together and give projects. These are funded for typically two years. We also have implemented a PHCE seminar series that twice a year we

bring in either outside speakers or speakers within the agency to discuss their projects, and we'll have the call for new proposals coming up in June. So we were able to fund 13 projects this past fiscal year. Then we have four second-year studies.

I wanted to give you a snapshot here of the projects and really just showing you the breadth of projects. These are projects that CBER has the PI, these may be collaborative efforts across the various product centers, but the PI is actually from CBER in this instance, and these slides that I'm going to be showing you indicate where the PI is located. You can see dealing with the SARS-CoV-2, exploring the Zika virus.

These are ongoing PHCE studies where CDER is heading these up, looking at lactation PBPK models, also pregnancy exposure registry-enrollment projects. So not just lab-based type projects, but we also have in silico projects. Here's one using modeling and simulation tools, evaluation of NAMs of folliculogenesis for assessing toxicity.

These are more CDER projects. Also, a project at CDRH looking at radiation dose for pediatric patients.

These are our four projects at NCTR that were funded this past year. So again, looking at drug-placental permeability, assessing neuro-tox that makes opioid

medication-assisted treatments, and also some cannabinoid CNS work as well.

So I do want to put in a plug for our Global Summit on Regulatory Science. NCTR has really headed this effort up for the agency since its implementation and had a very successful meeting last year in Singapore and then the 2023 meeting would be held in September in Parma, Italy. Myself and Dr. Tong with DBB and George Kass at EFSA there in Parma, we are right now developing the agenda for that meeting. But the focus is going to be on NAMs and new alternatives and some of these emerging technologies. So I know it will be a very, very fruitful meeting this year.

So I'll finish up. I wanted to just talk about some of the hurdles that we face, not just down at the division level, but this is something for the entire center that we're facing. More than half of our research is at the direction of the product centers, but there is this misperception that all of our research is being funded by the agency through other mechanisms, but actually, the majority of our work that's funded here is through our budget authority.

One of the issues that we have with our research is sometimes the external funding often comes very late in the fiscal year. So it's this feast or famine issue, and so when you need to close things out, sometimes by mid-

August, to end the fiscal year so our financial folks can get everything closed out and we don't get money until June or July, that puts a lot of burden on the staff to try to get things ordered and work done and supplies ordered that late in the fiscal year.

Also, each funding program that we utilize has different purchasing constraints where there is no equipment on this project or no billable hours on this project, and so we have to juggle that. This past year, our BA was $76.3 million and that was an increase over the previous year, but also other issues increase, of course, payroll, contracts continued to go up, and also our TAPS coming from headquarters continued to increase as well. So just a smaller and smaller piece of the pie that we seem to be having for our discretionary money which is what we use for our internal research.

In FY23, Congress provided about $3 million towards our predictive tox roadmap work, but our actual research in that area, if we fully funded all of our projects, is about $22 million. So you can see there was a big shortfall there in the projects that we had that could go to towards the PTR.

Also, some of the other hurdles, of course, and I'm kind of preaching to the choir here, I know people in the academic environment as well as industry, they're

having problems hiring because of the applicant pools. Low unemployment is great unless you need people. It's great for the worker who can jump from job to job and know if they quit this job, there is probably another one waiting on them, but it makes it difficult when you're hiring in that environment. So sometimes our applicant pools have been very low for our jobs that have been advertised.

We have a timeline for Title 5 which is our GS employees. Typically, six to nine months from the time of when you need a person to when you get them onboard. So that makes it tough to bring someone quickly in to try to work on particular projects.

Now, we're competing of course with remote options that are offered both inside and outside the government. That's one of the first things people ask now when they're applying for a job, does it have remote capability?

Converting visiting scientists and staff fellows to FTEs, sometimes there are issues there. Also, hopefully we won't have as many constraints moving forward with our ORISE, but we do have constraints in that because that is a contract that has to be funded on an annual basis, but we recently moved that into the FDA working capital fund, so hopefully that will help us in terms with our timeline in

trying to hire those applicants, those fellows. I think that's it.

DR. GANEY: Are there any questions from the group?

DR. GANEY: I'll start off. I do have a question. Tucker, you mentioned that some projects have budget constraints, you can't order equipment, you can't bill hours. How are those constraints set?

DR. PATTERSON: It depends on the funding mechanism. A lot of times, there's not a lot of money that comes with the funding on certain projects. Unless it's coming from CDER or some of our product centers, they will typically fully fund a project, but again, it's within the fiscal year. We're still kind of bound by those fiscal year restraints so we can't carry money over from one fiscal year to the next.

But some of these internal funding mechanisms like through our Office of Women's Health or Office of Minority Health and Health Equity, there are restrictions on that about how the money can be used. It can only be used for, say, discretionary for supplies, some say you can't purchase equipment because the amounts typically are not in the range where you could buy a $250,000 piece of equipment with the money that's coming in. So you really

have to juggle that, and again, you're kind of waiting sometimes toward the end of the year.

One of the things that the agency recently did which I think will help us tremendously is with these internal projects now, they're going to not fund these until the beginning of the next fiscal year. It used to be you went through the whole application process and you don't get the money until about midway through the fiscal year. Now the applications are going to be due in FY23 but they're not going to be funded until FY24.

So that's going to give our researchers hopefully about 10 or 11 months to get those funds spent and they can get a little bit better assessment of what they're going to need through the course of the year. So I think that will help us tremendously because when you get funds in April, May, June, and they have to all be spent by August, it's just this very hectic time for NCTR, those last couple of months of the fiscal year.

DR. GANEY: Thank you. Does anyone else from the SAB have any questions for Tucker?

I have one other question which relates to the roadmap. Does NCTR have a timeline of milestones within that roadmap for themselves? Like, by the end of 2023 you want to have this many protocols and by the end of 2024 you want to have something else?

DR. PATTERSON: Not so much the metrics in terms of numbers, but within some of these things that we're developing, we're working with the product centers to say, hey, we want to have this done. A lot of these things are very time-sensitive. We want to have answers sooner than later.

Our projects now are really migrating towards more short-term projects than these three-, four-, five-year type projects. We want to have answers a lot more quickly than we have in the past. So we're really looking at that pretty closely within the Office of Research. When a PI submits a project, typically the rule of thumb is a three-year project. That's just been the way it has been at NCTR for many, many years since I've been here.

Now we're looking at these things a little more critically in terms of, well, is it really going to take that long to generate this data? I mean, can we push this up and make it a two-year project instead of a three-year project? Can we have all of our lab work in the first year and maybe have some of those milestones reached a lot quicker than down the line?

Especially in an area like CBD, we know that this area is going to change. We're going to have different guidance probably within six months on the CBD area. So we want to be ready to respond and we want to have data in

hand and not say, well, now that the agency is ready to have this data, give us a couple more years and we'll have the data for you. We want to be proactive and try to push these timelines up a little bit more in some of these areas.

DR. GANEY: Thank you. Well, if there are no other questions for Tucker, I'm going to invite Alex to give us a subcommittee review of the Division of Bioinformatics and Biostatistics.

Agenda Item: Subcommittee Review of Division of Bioinformatics and Biostatistics

DR. TROPSHA: Thank you, Patti. Thank you for showing the slides. We have provided this review to Donna and shared it with DBB. I thought it might be easier if we go over the review using slides. So at least people have something to look at.

Just a few introductory comments. This is just for the record, the composition and expertise of the committee. Patti and I co-chaired the committee and members also included Anne Pariser, former with NCATS, currently with Alltrna, Ken who is currently in the room, and Hongmei Zhang from the University of Memphis.

We divided the duties, as I will describe shortly. The division has presented the summary of the work and five focus areas. So we have divided the reviewer

responsibility and written the review, with one person assigned as a primary reviewer and a second person assigned as a secondary reviewer. I have compiled -- Patti and I have compiled the final summary of all reviews, all the reviewers have read and signed off on the final review that we have submitted to Donna after completing the job.

We basically went over the materials that were presented to us in writing, as well as said at the meeting which took place May 19-20 of last year, about a year ago, and we based our reviews on the analysis of the booklet that was provided to us, as well as presentations given over two days of the meeting.

The booklet included the division overview and then summary of divisional research and support, and then this year -- and I think it was different from the previous review that took place in 2015, we've been exposed to the summary of five focus areas rather than reports or individual sections of the division. We've been given access to bio sketches, analyzed previous review that was done 2015, and then after the committee meeting, we asked Dr. Tong via Donna for additional information to clarify the divisional capabilities in the area of CPU and GPU computing, and so we were very quickly given the summary of this information. So thank you, Dr. Tong, for providing

that extremely quickly. We felt that we had very rich information to base our review on.

The review was organized sort of following the presentation format and the booklet format. To comment briefly on the overview of the division, was established in 2012, and had undergone one previous review in 2015. At that time, the division consisted of three branches, Bioinformatics Branch, Biostatistics Branch, and Scientific Computing Branch. Then following the previous review, the division established a new branch in 2017 called Research-to-Review, R2R, led by Dr. Joshua Xu. That was really established in response to previous review, but also to reflect on the importance of the function of the division to the FDA.

At the time of the present review, the division consisted of four branches, Bioinformatics, Biostatistics, R2R, and Scientific Computing, and then Dr. Tong formed some time prior to the meeting an immediate office which also has certain research responsibilities going on.

The personnel is spread across four branches and immediate office. It includes government staff, which is research scientists and support staff, has doctoral fellows, graduate students. We also noted that at the time of the review and hopefully the situation has changed, the division had 10 vacancies, kind of reflecting what Tucker

just described as a challenge in recruiting personnel, and so hopefully Dr. Tong will address this issue of vacancies, given the enormous amount of work the division should be doing.

Just to finish this overview, division is described as an indispensable resource to the FDA in the areas of bioinformatics and biostatics and its mission to assist the FDA in the review process, strengthen linkages with centers, evolve its capabilities in tune with agency needs, and with that mission as really well-defined and represented and attended to.

The division staff is roughly divided 50-50 between working on research and support. That as we understood formally relates to different career paths for the personnel. Predominantly, the research is in the Scientific Computing Branch and the immediate office of the Branch Director, and then support is distributed across the other three branches.

Since the 2015 review, the division has undergone substantial changes. Two senior leaders, Drs. Perkins and Chen have retired. The new branch was established, new leaders have been appointed for each branch, except for the scientific computing, and the division also increased its support of the ORISE program to recruit more postdocs. It's also working to establish an institutional agreement

with Arkansas State University to recruit more graduate students to work on projects of interest to the division. R2R branch is very active in fulfilling its mission and expanding its collaboration with multiple FDA Centers and also an important change that was highlighted in the presentation, on behalf of the division, is the establishment of the artificial intelligence research force, abbreviated as AIRForce. Just parenthetically, I think that all the abbreviations are extremely clever and easily memorizable. So that is certainly probably Weida's ingenuity in doing this. So I will not read all the abbreviations, but just point that out.

So the review starts with general comments for the division. We have noted that the report was very rich, reflected on multiple projects that were aligned with the overall goals of the division and it's really fulfilling its mission to support regulatory science research in diverse fields that are critical to the FDA mission.

There are a lot of projects. So I think ten were included with six FDA Centers. The division has been extremely prolific in publications, 25 to 35 papers per year in journals with an average impact factor of 7 and 14 citations per paper on average. So that would have been IF of 14 formally calculated.

Training mission, the division trained more than 110 graduate and undergraduate students, postdocs and professionals, multiple internal awards. So our overall assessment of all the activities within the DBB is that the achievements have been outstanding in all major areas, including basic research, collaborations, training, and support of other centers.

Next slide, please. Before I go there, let me just say overall the recommendations and then I'll go into individual areas of focus areas that were presented in the division overview. So overall recommendations, the division, we observed that the division has been an extremely valuable resource, both for FDA research communities at large. Clearly as the importance of data science and AI presently appreciated by both agency and external research community, the demand for the expertise in the division is likely to increase. So we have noted with the large diversity of projects, it would be helpful for DBB to establish clearer approaches for project selection and prioritization. The current approach for that was not made clear to the scientific advisory board.

It's very obvious and commendable that the division has achieved recognition and growing recognition by multiple centers within the FDA, recommendation is that it would be helpful to outline in greater detail how DBB

collaborates with other branches within NCTR. We have noticed that most of the discussion was linked to external collaborations between DBB and centers within the FDA.

It's certainly great for DBB to establish stronger working relationships with ORISE and Arkansas State University, because it enables the division to effectively recruit additional minds and hands to work on important and interesting projects, and it's quite clear that the projects conducted within the division classify and qualify as important interests and it would be advisable to continue in this direction and consider making similar strategic arrangements with selective academic institutions across the United States.

We've also noted that the division had achieved prominent recognition within the FDA as reflected by multiple awards, as I noted previously; 12 awards were received by scientists within the division. We find it's important and highly advisable to increase the visibility of the division and its members at the national and international levels, increase collaboration with external researchers outside of the agency, and promote the distribution of databases and tools via specialized publication types. Given the amount of databases and software, research software the division produces, there are avenues to publish these types of works in several

journals, such as application notes or database issues supported by nucleic acid research that we recommend that the division considers this additional avenue, avenues, to disseminate data and databases and software.

The report provides information about cumulative successes of the division and average productivity by the DBB staff. We recommend that for the purposes of fair productivity assessment and career advancement, it would be helpful to outline metrics by which each DBB staff is assessed individually.

Next point is the division supports multiple projects important for the field of regulatory toxicology, including the development of multiple computational toxicity prediction models. These models are disseminated by research publications and presentations at research meetings. It would be important to outline specific steps towards making such models into accepted regulatory tools that are used routinely by the agency. So that's sort of a comment on the importance of translational regulatory science.

Finally, because of its demonstrated and well-supported value to the development of regulatory science at FDA, the division is encouraged to continue its outreach to other centers, offices, and divisions within the entire agency. The work done to date is potentially extensible to

other areas that could open up new areas of collaboration that contribute to both DBB and FDA's mission.

I feel that it's important, so I didn't include this on the slides, but these recommendations, all recommendations, are initial part of the report and I thought they should be read here, and hopefully addressed in Dr. Tong's presentation later in full.

So now I'll go quickly through individual focus areas. First one was regulatory applications and support. We noted that there are multiple collaborations. For each focus area, there are three slides, an overall assessment, research projects, and overall conclusion.

Overall assessment of focus area 1, regulatory applications and support, fully consistent with missions and goals of the division. The division had initiated and supported several regulatory application programs. These programs played a major role in advancing the adoption of emerging technologies within the FDA review process. It supported training and education of FDA review staff, and it also helped FDA to track, summarize, and search this information to better inform this work, and the value of this focus area, perhaps primary focus area within the division, as evidenced by the large number of awards and dozens of peer-reviewed publications with hundreds of

citations each year, so overall this area is assessed as excellent.

Specific projects that we reviewed. So the way the slide is organized is that we did not have any critical comments or suggestions beyond the overall recommendations that I just reviewed, and this is just briefly bullet point summary of the scientific projects, just to reflect on the richness of the projects. So there were five that were discussed and presented, including collaboration to integrate machine learning and NLP to assist information capture from FDA reviews and labeling, development of the Automated Laboratory Information System, advanced semantic indexing techniques for the Center of Tobacco Projects, several projects with the Office of Translational Science, and several exploratory projects with FDA Centers to identify areas with unmet need by applying AI to research documents by category and to search patient narratives.

So these are all important projects highlighting and reflecting the growing use of machine learning, NLP, AI in document processing, very up-to-date modern research. So no comments there.

Overall, in this area, a remarkable amount of work on behalf of multiple FDA Centers, all done in a relatively short time. Many IT/machine learning/AI tools to accelerate and automate what used to be a highly

laborious search, capture, and assessment of large volumes of information and obviously high level of interest, user acceptance, rapid uptake by FDA staff. So all good there. We just kind of have supporting recommendations: to continue to find ways to expand this work essentially across the entire agency and continue close integration with the offices of the division to make DBB even more relevant to the FDA and NCTR missions. But we consider this area of primary importance for the entire agency and certainly a great area of research.

Area 2, alternative methods, and knowledgebases. So this is sort of the backbone of many activities across DBB. The division has developed a variety of different knowledgebases to be used by FDA reviewers, is actively developing alternative approaches that rely on AI and machine learning, and it's clear that the work is important and related to the missions of both the center and FDA, and the quality of science and supporting role of this area is very high.

Specific projects involve the development of multiple knowledgebases. Some of them are listed on the slide. So I'm not going to read this. Minor comment: it was in the presented materials sort of uneven description of what is done with the databases. So for some databases, there is active cheminformatics work that lists chemical

structure and related activity, and for some of the databases, this analysis has not been done. So minor comment that it would be important to have consistent way of creating, organizing, dissemination, and analyzing the content of those databases.

One of the models that the division has been advancing consistently is to predict drug-induced liver injury to support the FDA review process. The presentations were sort of more on the academic side. Was not made clear how these models would be used in the review process, and we made these comments several times, and again, I'll briefly emphasize here that it's important for the division to push models, and I think now is sort of better and better time to involve alternative in silico methods in regulatory review process. So that's part of our recommendations.

Clearly, models developed with deep learning and machine learning facilitate alternatives to animal testing, was not clear how the model is intended to be used. If it's to be used as an alternative to animal testing, this kind of resonates with the previous comment, the criteria for applicability need to be defined. So again, kind of push models more as regulatory assessment tools.

And then there's a project, AI as alternative approaches in nanotoxicology using machine learning and

deep learning. This is of natural interest in the computational research community, and one of the questions that is interesting and the division is addressing and we encourage to continue to address this question. Deep learning as a more recent approach still needs to be validated in terms of its applicability, the different types of data and datasets. So it's certainly important to continue to explore whether models developed with deep learning offer advantage as compared to models that use more traditional earlier machine learning techniques.

Summary, work in this focus area has been very intense, again highly relevant to the mission of the division. We recommend expansion of curated knowledgebases, making these accessible to the research community. Those databases, and this is sort of close to my own area of expertise, are highly curated and effective for building benchmarking predictive models for multiple endpoints. So increasing, that kind of resonates with early observation that we recommend greater dissemination of the accessibility and availability of those databases.

Research community, similar. Recommend making models accessible, for instance by sharing models via GitHub, and again, the emphasis on the use of models as alternative methods, achieving regulatory tool status, for instance registration, there's sort of a new potential to

register computational models with MDDT program, run by the agency. So that's also a recommendation as to how to expand the work in this area.

Area 3 is precision medicine and therapeutics. That's really an important area for the center and for the entire agency. Many activities directly advance priorities in this area. It's been significant progress in developing AI and machine learning models for a broad range of endpoints that are critical to drug safety evaluation, specifically liver toxicity, carcinogenesis, mutagenicity, cardiotoxicity. There has been considerable progress in aligning this work with the stated mission of NCTR and that in part was also in response to the previous review.

Overall, commendable efforts to improve pathology workflows, taking advantage of AI-enabled digital pathology platforms. So highly plausible assessment.

Specific projects that were listed and we commented on. The first project that's been sort of one of the key projects within the division for years, and that's supporting writing international consortium of Microarray and Sequencing Quality Control, focus on development of quality control metrics, reproducibility, and benchmarking. This has been a traditional longstanding area of research and ongoing project. Minor comment is that the division should consider the degree to which this effort has been

coordinated in collaboration with academic stakeholders and other government agencies, and that's just a reflection on the significance of supporting this consortium.

The next scientific project is development of statistical tools for regulating deep sequencing-based testing, and that's the collaboration with scientists in different offices and centers within the FDA. We note that plans to focus on clinical utility assessment is appropriate, but it's not specified the extent to which these efforts will be carried out in partnership with clinicians. So that's just again a minor comment and recommendation of the direction to emphasize.

Next project is therapeutics, focusing on development of AI methodologies to identify existing drugs as options for treatment of current and future pandemics. So no need to overemphasize the importance of this area of research into this world.

Drug repositioning for rare diseases, taking advantage of AI-powered frameworks. This seems to be one more to sort of scientific inquiry. In general, not clear how this overall effort fits into the mission of NCTR and FDA and if this will be continued. It was not clear from the analysis as whether this is sort of a side project of temporal interest, and whether it's going to continue or close. So some clarification there is required.

And then it was an emergent project on the early science of sex differences in adverse drug events.

Overall summary, the focus area is generally well-aligned with the division priorities. Dr. Weida Tong oversees this effort and continues to provide outstanding leadership for his team. Overall, clear evidence was provided of the collaborative nature of this program.

So AI and machine learning, so that's sort of basic focus area. Overall, this has been a focus area of interest for the division for a long time, which is methodological development and use of machine learning algorithms to address problems in chemical toxicology. This, there is a very -- I guess I don't need to comment much -- we see enormous amount of interest in using AI deep learning machine learning techniques to analyze rapidly growing datasets in every area of human activity, of course including rapid growth of chemical toxicology databases. So it's a proper focus on the implementation of AI techniques to improve and enhance the efficiency of regulatory operations, and it's a critical area for the center and for the agency as tools and methods and methodologies and software developed with the use of AI and machine learning fuel many applications in other areas. So in our mind, it is kind of in the same category as forming and disseminating specialized databases.

So multiple specific projects, material projects, have emerged that rely on advanced processing of textual documents, such as FDA labeling documents. So that's one of the ongoing active ongoing projects, and it's an interesting effort to develop a pharmaceutically relevant version of BERT which is one of the major NLP programs. So that's likely to be rewarding. That's a very interesting project.

DeepReview, which is an information retrieval system powered by natural language processing and there is an expectation stated in the documents we reviewed and to our mind that this broadening use of this tool is expected. We found that the dividing NLP developments -- so the first and second bullet point of two separate areas -- may be somewhat artificial, but I guess that can be handled internally.

SafetAI is also an important project to support the initiative to enhance the IND review process. Technical challenge is to establish the utility of these models and their advantages versus the application of traditional ML techniques. Explainable AI, that's certainly everybody working in the area of AI is interested in making the black box explainable. It's still a point of addressing the utility of models for various endpoints as compared with simpler models, and then we've noted there

are multiple projects that have been developed in this area and I'm sure very diverse projects will continue to emerge. So there are a few projects under development listed, all very interesting, and hopefully we'll hear about the implementation as time goes on.

So a highly important area and should remain a major component of the research portfolio within the division. It's certainly obvious that members of the division continue to stay at the forefront of using modern data analytical methods as applied to problems in computational and regulatory toxicology. As mentioned several times, it's important to kind of go beyond the hype and establish relative value of emerging approaches in comparison with more traditional techniques and it's important that the division is doing this to continue to promote databases and tools created within the DBB across research community, both within FDA and at large.

Real-world data, that's a relatively new focus, but it's highly important for FDA, and I think the analysis of real-world data is also fueled by methodologies developed under focus area 4. We've noted a new grant that Dr. Wang received, an intramural grant, from the Office of Minority Health and Health Equity. The project is in the beginning, so it was only awarded in 2021. Not clear if anything has been published yet, but it's a new project,

and it appears to be a highly promising emerging area of expertise within the division.

DR. GANEY: Alex, I am going to interrupt you for just a minute. You have two minutes left to wrap it up so we can vote.

DR. TROPSHA: Let me wrap -- I think there's two last slides. So let me just be brief here. Several scientific projects, all interesting and of relevance to the division. There are a couple, as you could see, a couple of recommendations made with respect to individual projects, and some of them are technical, especially the use of propensity scores for drawing final conclusion for association between ethnicity and critical care delivery, but again, the projects are relatively in the beginning.

Just one overall recommendation. Link each project with FDA's overall strategic plan and hierarchy of FDA's priorities.

I think that's the final slide. So, overall as mentioned in the beginning, excellent progress within the division. Some points of concern. From the materials we have been exposed to, the budget provided to the division was significantly reduced in 2021. I think there is an explanation for this, but it was not clearly discussed at the time of the review. At the same time, the importance of the work within the division is growing, the staff had

grown by 10 from 50 to 60. Again, I think it's very clear and I think it's clear from our analysis that there are emergent new focus areas and growth of data, especially omics data, real-world data, so the need for robust AI techniques to support multiple projects within FDA necessitates the recruitment of additional manpower, and so the staffing and funding for the division should be very robust and perhaps growing.

There have been five vacancies, not including the Scientific Computing Branch. That indicates difficulty in recruitment, and again, Tucker addressed this in the opening remarks. So hopefully we will hear about specifics how this concern is addressed from Weida's presentation.

That's the last bullet point. So that's it. I think I am within the timeframe.

DR. GANEY: Thank you. That was a very nice summary of the report. Ken, you were on the committee. Do you have any brief comments you want to add to what Alex had to say?

DR. RAMOS: No, not really. I think Alex did a good job capturing the essence of our discussion. I look forward to hearing what Weida has to say.

DR. GANEY: Okay. Before we get to that, the Scientific Advisory Board is asked to vote on whether we accept this subcommittee report. So I'm going to ask all

of the Scientific Advisory Board -- maybe I'll just go around and you can tell me if you are in favor or opposed or abstain.

(All accept.)

DR. GANEY: So it is unanimous to accept the subcommittee report.

Thank you, everyone. Thank you, Alex, for staying on time. We actually have two extra minutes. I thought that would take longer. We will take a break now and resume at 11:00 when we will hear Weida's response to the subcommittee report. Thank you, everyone.

(Break.)

Agenda Item: Response to Review

DR. GANEY: Welcome back, everyone. I will yield the mic to Dr. Weida Tong for his response to the subcommittee's report.

DR. TONG: Good morning, everyone. My name is Weida Tong, and I'm from the National Center for Toxicology Research, and first and on behalf of my division I would like to express my sincere appreciation for the efforts and the time that subcommittee members have spent interviewing my division and the text of Alex Tropsha and for his leadership to conduct this review.

Last year, we provided a lot of the materials which really take a lot of time to go through all of these

materials. However, in return, we received a very high quality of the report from the subcommittee and ranging from recommendations and suggestions and critiques. So clearly the quality of the report demonstrated the devotion from the subcommittee members and for which we are really, really appreciative and very much grateful.

Now we take these recommendations and suggestions as well as the critiques very seriously, and they will guide our future research and support activity in the division.

Just a disclaimer.

Just a quick reminder that the division consists of the four branches. These are the Bioinformatics Branch and Biostatistics Branch, R2R Branch, and Scientific Computing Branch. Now Scientific Computing Branch was not reviewed, and since this branch is the centralized resource to provide IT support that the entire NCTR.

So what will be addressed in this presentation? First, I'm going to tell you what will not be mentioned in this presentation. The report has a lot of positive comments about the division's accomplishments in both areas of research and support. We appreciate very much these positive comments. They're certainly, these positive comments are a tremendous encouragement to the division

staff. However, I'm not going to mention them in this presentation.

It also has many, many recommendations, and valuable suggestions, and we totally agree with, and definitely going to pursue. So I'm not going to repeat each of these recommendations in this presentation either. Some of them have already been mentioned in Dr. Tropsha's presentation. So in terms of my presentation I'm only going to address these comments that need clarification and further explanation.

My presentation is going to be divided into two parts and the first is just address the general questions and the second part is getting to the specific focus areas. This very much follows the same format of the report we have received, and also very much outlined in Dr. Tropsha's presentation as well.

Okay, so part 1, we're starting the general questions. We have eight of them, and we are starting question number 1 is about whether DBB should establish a clearer approach for the project selection and prioritization. This is a really interesting question, and usually the project selection and prioritization has been traditionally handled at the center level, which normally involves two steps. So first we develop the concept paper. Once the concept paper is approved by NCTR and then we

proceed to develop the full protocols. In both steps we involve the review from our sister centers.

At the division levels, usually the division director is a gatekeeper for the protocol to enter to the NCTR protocol systems. So since our division is mainly emphasized on everything we do should have some relevance to the FDA regulatory applications. So the DBB PIs are advised to follow general guidelines, and I call these guidelines ICE principles. ICE stands for Impactful, Collaborative, and Expandable. Basically a division project should be impactful to the FDA's mission, collaborative with our sister centers, and expandable from the research to review.

I usually advise the division PIs before they put the concept paper in and have the opportunity to talk to me, at least I have an opportunity to explain to them and to provide my input on where the projects are supposed to go.

So next question is whether the division should establish fair metrics or fair mechanism to assess the productivity and to the extension of support of their career development. Well, again, the FDA does have a standard mechanism to assess the performance of a federal employee, which is called the Performance Management Appraisal Program or PMAP for short, and in this mechanism

a supervisor established a metrics which was first communicated with his subordinate at the beginning of the year, and then in the middle of the years they meet to discuss the progress, but in the end of the years, a score given to assess their performance. So this is the generic mechanism, has been implemented agencywide.

In the DBB, we do establish the metrics and we try to be as fair as possible for both research and support scientists. These metrics were tailored to their grade levels, and we also provide general instruction on the steps they need to take to move up to the grade.

The question number 3 is about the budget, and the SAB made observations and realized in 2021 we only received half of the budget compared to the rest of the years. These things happen, and we just had a very bad year in 2021. Actually so was this year. So this is an easy explanation, and I think Dr. Patterson sort of touched on these topics in his presentation, as well.

Question number 4 is about how we can establish a stronger retention plan at the FDA level to maintain the manpower to allow us to be more productive to proceed much more -- basically add more sustainability for the program we are pursuing. I couldn't agree more. We definitely need to have a little bit stronger retention program in the FDA, and particularly in NCTR. For our division and we

have been sort of facing a lot of these kind of challenges, just giving a quick example. Recently we have statisticians in the local university -- I'm not talking about a statistician from the east or west coast. It's a local university, and he wanted to conduct a little more research and he is starting looking for a job, so we approached him and we talked to him, and then we realized he was getting paid 40 percent more than the NCTR can give. So you can see the challenge we are up against, and we do not have a specific mechanism really kind of competing against industry, even the local university, particularly for the area we are in like statistics, statisticians, computer science and data science and so on and so forth.

So what we are doing right now, we just recruit a lot of the postdocs and graduate students, so when the turnover happens we will be able quickly to fill that vacancy so we can add a little bit more sustainability into our program.

Question number 5 is about how we conduct collaborations with other divisions at NCTR. These collaborations normally it's grassroots efforts. The last times I checked, for the DBB-initiated research projects, around 60 to 70 percent were involving the collaborators from other divisions at NCTR, and equally our scientists are routinely being invited by the PIs from the other

divisions to help out their project as a co-PI and particularly in the area of bioinformatics and statistical analysis.

So those are the grassroot efforts, and we did not really rely on the top down sort of mechanism. But in some areas, we do, and for example we realized genomics has become really important tools and in the center there are a number of groups involved genomics data analysis. They really need bioinformatics support. So for that we have developed and are maintaining the critical infrastructure and platforms such as like the Galaxy platform for the genomics and to support NCTR-wide research involving bioinformatics.

Okay, so this is a really, really good suggestions and we appreciate it very much. Basically the SAB members provide a broad range of the suggestions on how to increase the DBB visibility. We definitely are going to follow. I just am very happy to report and after the SAB review last May, we did make a lot of the efforts. For example, the DBB senior leadership, including all the branch chiefs and me, were invited to present close to 20 presentations at the national and international conference. In May 2022, we co-organized the workshops and called Cheminformatics Resources of U.S. Governmental Organizations at White Oak of FDA. In the same location,

we also co-organized the fifth annual conference of the MAQC Society in September, with chief scientist actually has come up to give opening remarks for that conference.

In the same month, September 2022, we also co-organized the American Statistics Association Biopharmaceutical Section and by focusing on the regulatory industries that statistics workshop.

Okay, so this is really good questions. I'm very glad that this question has been raised so I have an opportunity to explain a little bit more on how we translate our models into the regulatory applications. At this point, we try three different pathways. The first one is the consultation, and basically we develop the model internally and then we communicate with our reviewers, particularly in CDER, about our models and if they see the value from our models, when they do conduct the review process, they can send the request to us, ask us to provide the assessment, particularly related to the drug-induced liver injury.

The next slide I will explain a little bit more about this consultation. This is probably the most successful mechanism that we have so far. As you may already realize, there is a lot of sensitive data in the FDA, and those data is not available even for us. For example, we work with CDER, we are not able to get into the

CDER system to access these sensitive data. So at this time, we are working with CDER to set up a secure environment and then we can deposit the model in these secured environment, and then we can use these models to give a prediction for these compounds and drugs and submit it to the CDER review process, and we are still working on it and I'm not going to claim it's already been successful, but it seems like this is a very good pathway for our future translation of the models to the regulatory application.

The third mechanism we also tried is related to ISTAND qualification program. ISTAND stands for Innovative Science and Technology Approaches for New Drugs, and this program was established by CDER to qualify the tools and the methods for the regulatory application, also to facilitate drug development, and once these tools are being qualified and the data generated by these tools, and then no longer need further confirmation, and directly and into our regulatory applications. So this is a tremendous incentive to pursue that kind of mechanism and looks like this mechanism is going to be available to the internally to the NCTR as well. So we are certainly going to pursue that mechanism as well.

So the next one is just a quick summary about the consultation we have conducted to support the CDER review

process. As of December 2022, we already did a consultation for 57 drug applications, most of them from the IND and some from NDA. On the right side shows what particular divisions from the Office of the New Drugs of CDER to make these requests.

This is the last question in part 1. This is the one about more specifically on the Biostatistics Branch, and in this division, and the SAB members make very good observations and the SAB find out that our Biostatistics Branch was focused entirely on the research. It's not as we reported back in 2015, which is sort of a split between the research and support, and between research and support, and for this I have a very easy explanation. In 2019, NCTR conducted a center-level reorganization. So the supporting unit from our Biostatistics Branch was moved to the Office of the Scientific Coordination to strengthen the support activity towards the entire NCTR. So during that period of time, we also experienced a tremendous turnover in the biostatistics branch, as Dr. Tucker already mentioned, we lost two former branch chiefs. They all retired, and we also have several people left at that branch.

So in last review, the old branch members are not present in the 2015 review. So these are new people. Of course, these new people bring the new skillsets, which also create a lot of new opportunities, so when we appoint

Dr. Wang to lead the Biostatistics Branch, he reoriented the focus of this branch by focusing on the real-world data and the real-world evidence which clearly is the focus in the FDA.

All right, so, this finishes part 1. Now I'm going to move to the part 2. I'm going to get into each focus area and focus area number 1 is related to the regulatory applications and support, and there is one specific comment I would like to address in this focus area.

The comment is we should do a little bit more to expand our efforts across the FDA Centers, and we really appreciated this comment and just wanted to mention that since the site visit in May 2022, we have developed an additional Smart Template for the CDER Office of Clinical Pharmacology, and I will explain a little bit more in this afternoon's presentation about why it's a big deal to add additional Smart Templates. I'm not going to explain here, because the time is limited.

We also had exploratory discussions with the CFSAN Office of Food Additive Safety. So we are definitely going to seek additional collaborations with FDA Centers and office and divisions.

Now I'll move to focus area number 2. It is about alternative methods and knowledgebases, and there is

a lot of wonderful recommendations, suggestions, in this area. So I am going to spend a little bit more time to go through all of that. First one, about the liver toxicity knowledgebase, which we have been working on for the past decades now, and we collect a lot of the data and the SAB recommended we should continue these efforts by incorporating additional factors, such as immune, genetic factors, into the database to strengthen the prediction by incorporating the factors related to host because when we talk about the liver injury, we are always talking about drug-specific effect as well as the host-specific effect.

So basically the recommendation is we need to incorporate host factors into our database to include the predictivity of the liver toxicity and the knowledgebase we are definitely going to extract the immune systems related in the genetic factors, associated with liver toxicity, and incorporate them into the liver toxicity knowledgebase to enhance the data scope, and we also will mine the genetic effects and mixtures related to the herbal medicine and dietary supplements from the public sources, including the public database and the literatures for improving the diversity of the data in the database.

The next two slides really talk about the opioid activity knowledgebase, and this is the first question. The SAB recognized this is a really important effort and

was encouraged to develop a variety of models to refine our thoughts and the modeling procedures to facilitate the treatment of pain and opioid use disorder, and we couldn't agree more. This is a really, really good suggestion.

So we are actively to implement the various QC metrics and to make sure the data to be included in the database with high quality and once we have the high quality and quantity of the data in the OAK database, we will then to apply to different machine learning and deep learning methods to develop the knowledgebase. One of the focus areas is going to be on the pain and opioid use disorders.

This is also related to the OAK database, and this is also really, really good suggestions. The SAB members and the suggestion as to looking to the chemical structure motifs, which are driving the model performance. This is some practice -- it's quite common actually in the cheminformatics area, but we have not really articulated very well on this particular aspect of the modeling process in this efforts. We definitely are going to do that, and I just want to point when we presented this work and this project did just get approved, so we are mainly focused on the data curation and the database development, and move in the future and when we apply the machine learning and the deep learning, we definitely want to establish the

causality and to identify specific feature significance which drive the model performance. Thank you for the comments.

This is about predictive models for the drug-induced liver injury, and SAB members were wondering how these models are going to be used in the review process. I think Dr. Tropsha also mentioned in his presentation on these specific questions.

As I mentioned early on, we have three different pathways to translate our model in the regulatory and applications, and the first one is the consultation and the second one is move the data and the model into the secure environment, and the third one is go through the ISTAND qualification process. But for this particular models, we propose using the PK data to improve our model performance and likely we are going to continually use the mechanism number one, that's the consultation.

Here there are two questions. The first one is because we use the sort of terminology when we describe our model performance. For example, some of our models achieve 60 to 65 percent prediction accuracy and we consider this reasonable. So the SAB members are wondering how we define this is a reasonable predictive power. This is a really legit question.

In my mind, this is subjective, not objective, and for example, if we develop the model to separate the male from the female and these are easy endpoint, and I really expect the reasonable predictive power should be more than 80, even more, 90 percent. Anything below the 80 percent I don't consider them reasonable accuracy.

But for the animal studies, there is a lot of noise in the endpoint that came out from the animal studies. For example, recently we compared exactly same study design for the animal study, but it's carried out by two different groups. Just look at the study, animal study results, and they only reach to 70 percent in concordance. So in that sense, if we predicted the animal endpoints and we feel 60 to 65 percent fairly reasonable. The bottom line is that reasonable that the words we use is relatively subjective. It's not trying to be an objective, let alone to be quantitative.

Next questions on the same paragraph is talking about the applicability domains, and we definitely agree with that, and just for the point of the clarification and the every models we develop so far is not intended to be used as is to support the regulatory applications. It is basically a screening tool to set up a priority for the follow-up experimental validation.

So next question about large versus small, this particular terminology we use when we provide a report to describe our models. This question is totally legit, how we define large versus small datasets, how we say it. Well, I feel this is still subjective. For example, just using the previous example, if you want to separate the male from the female, you don't need a lot of samples, and even just looks like only a very small number of the samples we consider is large enough to separate the male from the female, using different machine learning methods. But if you are dealing with a dataset with a very lower signal-to-noise ratio, do you really need to have a very large number of samples to derive that robust models.

However, in the context of the project we proposed, we are mainly focused on the large dataset and then we trim down sort of the segmented sequentially to reduce the data size, and to see the function of the data size versus the predictive power. So we use that terminology in that particular context, and I hope I explained it well on that.

Next one is a great question. It's about when we are supposed to use the deep learning instead of machine learning. I'm just going to use one of the examples I have in the next slides.

So, when we should be used, the deep learning, instead of the machine learning or vice versa. In my mind, and this really relates to explainability, which has also been touched on by the Scientific Advisory Board during Dr. Tropsha's presentation as well. In this study, we looked at Tox21 bioassays. In total, we have 65 different endpoints, and for each endpoint we are using 12 different machine learning methods and also on top of that we are using seven different chemical feature sets. So basically, for each endpoint, I have 84 models. So now we will be able to conduct the comparative analysis across the different modeling approaches, as well as the different chemical feature sets.

So what we found is all the methods are performed quite comparably. So in that situation, of course, we prefer simple method over more complex methods, such as deep learning, because the simple methods offer much better explainability. Also, we looked at the features, and clearly all the features perform quite comparably as well, and we looked at these features; some features it's much easier to explain such as like LogP. We know the LogP associated with hydrophobicity or lipophilicity and molecular weight we know is related to the molecular size. But some features are more theoretical and it's very difficult to link to some sort of the biology we are

familiar with. So in that situation, we are definitely going to choose the biologically meaningful features to improve our explainability.

The bring-home message is that we really need to conduct a systematic evaluation across the different methods and in the end of the day, we need to balance the statistics with the explainability.

This now we move to focus area number 3 related to precision medicine and therapeutics, and the first question is related to how we are going to collaborate with academia stakeholders and other governmental agencies to involve some of the consortium efforts we conduct, and particularly the crowdsourcing we have recently involved the precision FDA. Let's just address the last question. In terms of the precision FDA, and this is an FDA crowdsourcing challenge, and I'm not entirely sure; I have not discussed with them as to whether this mechanism allows to engage the academia stakeholders and other governmental agencies. But I do know we established the International MAQC Society which is that reference in the bottom. This society was established with a mechanism to facilitate the collaboration between the government, industry, and academia, and this society is derived from the MAQC Consortium. So in the future, we definitely are going to

utilize this society as a mechanism to engage academia and other government agencies.

So the next question is about rare disease, and SAB had a question about whether it's not really clear how this overall effort fits into the mission of the FDA and NCTR. I'm very glad Dr. Patterson mentioned from the agency point of view why this area is important. Here, I'm just adding a couple comments on this, and first to just confirm, you know, FDA does have active programs on orphan drug development and rare disease, and actually we have the Office of Orphan Product Development, right under the Commissioner. This program actually was governed by the Orphan Drug Act, which is a law passed by Congress in 1983, and through these acts the FDA put out about $40 million in the last year to develop the orphan drug options, therapeutic options, for rare disease.

So basically I would try to convince you that this project is very much in line with the missions in NCTR and FDA, that the link below you will find more information from the link below.

Now we will move on to focus area number 4 related to the AI and machine learning. The first question is about one of the in-house deep learning methods we developed, and I do apologize we did not really make that clear how this method works, and I'm very glad you've given

me another chance to explain this methodology here. Also, the follow-up question is whether we compared diligently with the traditional machine learning techniques. So I'm just going to give you an example to address these two questions at once.

On the left side, it's a cartoon to summarize how we do it and basically for dataset, we develop many, many models. To be more specific, we develop 500 models using different machine learning methods. Basically we generate a pool of the machine learning models.

Now, we are not the first one doing that. Many people are doing that, as well. But once it reached to this point, most of the people using some sort of consensus approach to combine the prediction from all these models, such as like winner take all, took the median prediction or average of all the prediction, so on and so forth. But the way we did is different, and we inject the deep learning AI method to combine these methods to reach the consensus.

Because the AI will be able to tailor the selection of the models back to the chemical structure they are predicting, so the performance improved. So this is basically this is the essence behind our deep learning approach.

On the right side is we did compare our models with the other conventional approach. For this specific

example, it's related to mutagenicity, and we compared with the KNN, linear regression, supportive vector machine, random forest, and XGBoost, which is listed in the bottom right. You can see it and we look at the prediction accuracy. We also look at the applicability domain of our models compared to other machine learning methods, and you can see our models perform slightly better than other machine learning approaches.

So the next question is about AI explainability and whether we should focus a little bit more on the feature significance, which is driving the model performance to improve the AI explainability. Fantastic suggestions and really like it. We have not done too much about it, but we did that before. So this is not something alien to our group. We definitely are going to do a little bit more on that.

I just wanted to point out and we already are doing this and for more on the natural language processing using the language models. In the bottom of this slide, these are the two papers we published recently, and one called InferBERT, another one called Deep Causality, and in both papers we are trying to establish the causality of the specific terminology in the document which contribute to the model performance in such a way we will be able to

establish the causality between the terminology or the observations, and with the outcomes.

This is basically the overall summary for this focus area. Some of the questions are already being specifically addressed. For example, when we develop a novel approach and we are highly encouraged to compare with the other existing method, particularly conventional machine learning method, and thank you for the suggestion. Definitely we are going to do that.

And the same goes to the natural language processing models we developed to support the agency, and I just wanted to mention that most recently, we have a proposal which was awarded by Chief Scientist Challenge Grant, and basically this is exactly what we are going to do. We are going to compare different language models and then we're going to see whether the specific models are going to show more advantage compared to other methodologies.

Also, we have been highly encouraged to promote the database and tools from our division and to approach the research community. Just wanted to point out, every publication and we always deposit our software, all of them, in the GitHub, and we also make the data publicly available. Everyone can access.

On top of that, we also have the dedicated website set up by the NCTR that usually is very difficult to find. So if you google it, type in FDA bioinformatics tools, or type in AI4TOX, which is going to lead you to our website.

So this is about focus area number 5 related to real-world data and real-world evidence. There are several specific questions, and question number 1 is related to the Charlson Comorbidity Index which was commonly used in the research community. However, in our proposal we tried to develop and specialize CCI for the American Indians, and so the SAB are wondering what is the specific advantage to develop such a specialized CCI comparing to the commonly used CCI.

We did a comparison and we found if we used the Charlson Comorbidity Index, the commonly used index, we only achieved 66 percent accuracy for the Native American populations, but using our customized CCI that we can reach to 73 percent.

Also, there is a question about the propensity scores. We sort of in our toolbox we use a lot.

DR. GANEY: Weida, you have 2 minutes left.

DR. TONG: So the propensity scores, and we totally agree with the SAB recommendation. We are definitely going to assess the robustness of this

particular score, particularly when trying to compare the minority population against the larger population in terms of adverse events.

Okay, so this is the last one. First of all, everything you hear from my presentation is not my alone. A lot of senior members from our division contribute to these responses. I also, again, thank the subcommittee members for their wonderful input and we really, really appreciate every comment you make and this certainly is going to be guidance for the future research.

Thank you.

DR. GANEY: Weida, thank you for that clarifying response and thorough response. I will open this up to the committee to see who might have questions or comments for Weida.

Alex, did you have something to ask or say?

DR. TROPSHA: So let me start. Weida, let me first thank you for a very robust answer. In my observation, our questions and comments allowed you to highlight sort of additional aspects that were perhaps insufficiently covered in the original booklet and your presentations, and I certainly appreciate the fact that it's very hard not knowing what exactly reviewers are going to look for or say to prepare a document that summarizes in your case, I think it was six years, because of COVID-

related delays. So it's a huge amount of information, and I think on my observation our comment areas allowed you to highlight some additional aspects and strengths of your work.

So I don't think we should focus on some relatively technical details. I think that we, at the time of the review, felt that really we wanted to provide some suggestions that might be helpful for the future research, and I think that you've responded to those suggestions that we made, in full.

I'd like for us perhaps to offer some kind of two broader issues and hear your comments and comments from your colleagues and other members of the committee. One, I think unavoidably, the talk about the budget and staffing. I know that that's a tremendous problem. I think everybody understands this. But of course, it resonates with the amount of work you're capable of doing and with the priorities that you could set for your division given there's this balance between available positions, and I think when you plan, you should rely on every member of your team, versus what you could do given that you're understaffed. So I think that that's really worth deeper discussion as to that's I guess for the entire center, for your division, how the reality may need to force you to

balance the priorities and specific projects that you conduct.

So in this regard, I fully appreciate your response concerning the rare disease. So certainly, we know that that's a priority for the agency. The question is, given the focus of the center on toxicology research and your focus on that, whether that is one of those priorities that you may need to sacrifice, if you will. We all are very interested, and many groups work on this, including mine. But this might be a sort of one of those cases of that tough decision, right? So that was that, the underlying comment. So I'd like you to comment on the budget, the balance of priorities, given the budgetary restrictions and the under-recruitment.

DR. TONG: Thank you for the questions, yes. So, I normally had conversations with the PIs when they propose a certain project, and there are two categories of the project normally presented to me. One is the externally funded. For example, a competing the intramural FDA grants and you're awarded, of course I'm not, certainly not in the position to say, hey, you should not pursue, because you will have a resource and from that intramural grant and to support that project.

So what I look more closely is the project required funding from the division level. I need to

discuss with them whether there is enough manpower and computational resources to support this project, and of course also we emphasize that whether it was relevant to the FDA, this is probably much easier to do, and whether it's going to have the potential to translate to the regulatory application. So those are the parameters I use for the dialogue with the PIs.

So this is how personally I feel to set up the priority for our divisions and projects. With that said, actually the majority of the projects in our division is externally funded. That's why we have quite a successful to bring external funding into this division, even in the down years. We still be able to maintain the productivity and the progress in this division.

I hope this addressed your questions.

DR. GANEY: I was just going to jump in because I had a similar question for you, Weida, and I think the budget is really only part of the equation, and the other part is the personnel. So do you ever have to take a pass on projects because you just don't have enough people or everyone in your division is overloaded or up to capacity? I think that's an equally important question.

DR. TONG: Good question. For the first one, in my mind budget is the resource, because we spend a lot of the money to hire the postdocs, and this is probably the

single most expensive in our division, items in our division, is the postdoc. So for us, if the budget fluctuated, we will not be able to hire a lot of postdocs. So when we engage the collaboration with the external parties and this is one particular component that we emphasize, so that's first.

The second is whether we turn down any project which we don't feel we want to pursue. Yes, but it's not happened often. We did -- in my memory, we did turn down a couple of the projects in the past, mainly related to the support area, because we have the support staff and these mainly are residing in the R2R branch. So bring us a research outcome at a particular models to the regulatory applications and require a lot of the efforts.

So sometimes a project comes to us, it's not the scientifically sound, because we still want something to have some scientific significance, and we turn down this kind of request. Yes, we did. For example, I just give a quick example. There is a request from the CDER to ask us to organize the old FDA guidelines, all the FDA guidelines if ever released to the industry, and put them in the database and put some sort of machine learning/AI on top of it so it will be easy to find this information and all that. At that specific time, we do not have the resource,

we do not have enough people to really work on additional work. So we decided to turn down that project.

DR. TROPSHA: Just sort of quick, and hopefully we could discuss this further. It's on the same theme of funding, personnel, and priorities. This is my personal opinion, but I think in the next five years, right, we're going to review the division again in five years. You will see growing pressure for the skillset and contributions, and this is the reflection of this overall -- I don't know if it's revolution or however you want to call it -- pandemic of AI.

(Laughter.)

I mean, we see it everywhere, and there is strong pressure on people trained in this area, to train others, to contribute tools, methodologies, et cetera. So with that pressure, I expect this pressure to increase internally, which matters the most, and again, the question is and recommendation is to be prepared for you might be seeing this already, for this wave of requests and wave -- like the NLP stuff that you start to develop is one example, right? There's going to be more and more of that.

So somehow the division and the entire center should be prepared to respond plausibly and forcefully to this. So I think that I just would encourage everyone, including the center leadership and FDA leadership to

expect this, look into this, and help you with staffing and recruitment. Kind of my general comment. Address the fear of the future.

DR. TONG: Thank you very much. We definitely badly need it, and I totally agree with you. There is a tsunami of requests, and I just had on the phone with CBER a couple weeks ago, and they have like 10,000 images from the clinical setting and want AI to wrap up that and we just starting to have this conversation. Yes, totally agree with you.

DR. TROPSHA: Et cetera, et cetera, and also as we discussed increased visibility, I actually saw you have the distance of SOT. But I think more and more presence.

DR. GANEY: Okay, it looks like Cheryl might want to make a comment. We have time for at least one more comment.

DR. WALKER: Yes, and I just want to reinforce what Alexander said. John Weinstein once commented that decades ago you had one bioinformatician for every five or ten scientists. We are now at the point where you're needing to have four and five bioinformaticians for every one scientist. It is just the way it is going everywhere, and getting out in front of this is really, really critical. And you will have to pay more. You all are not even in as advantageous a location as we are in Houston or

Baltimore or some of these other places, but you can't keep these people. So paying extraordinary salaries is absolutely what is going to have to happen, and you can't get enough of these folks fast enough to stay in the game. So I totally am supportive of that.

DR. TONG: Thank you to feel my pain.

DR. GANEY: Are there any other comments for Weida or questions for Weida?

Well, this issue of hiring for people at NCTR seems to be a perennial one. I think we visit this every year, and maybe we need to think of this a bit more creatively in how we can help you to not just recruit but retain people with the expertise that you need, because you're doing great stuff.

Okay, thank you. I think now we are ready to hear from the FDA Chief Scientist if she is on board with us. Welcome, Dr. Bumpus.

Agenda Item: Statement from the FDA Chief Scientist

DR. BUMPUS: So, thanks, everyone, and thanks so much to the SAB for all being here and all your partnership. I'll just say a few things. I don't want to take up too much of your time.

I began last summer, August, as Chief Scientist at FDA, and I'll say really of all the things I've been

able to participate in so far, really one of the things that's excited me most, have been most rewarding, and really keeps going day to day is the relationship that I'm able to build and building with colleagues at NCTR and learning from their work and having the opportunity to be engaged and invited into their work.

So it's really been an honor and a pleasure and we thank the SAB certainly for their partnership on helping us to continue to bolster the work that's done and I think you probably have all heard -- I'm just joining the meeting now, but I just want to of course say that I'm particularly enthusiastic about our appointment of Dr. Tucker Patterson as the NCTR director and really look forward to NCTR reaching even higher heights under his leadership.

So I know I think several of you, but not all, so I'll just say I'm a really guess a molecular and translational pharmacologist. I spent my career focused on drug metabolism and trying to understand interindividual variability between people and drug outcomes really at a molecular level. So we did things like trying to identify cellular signaling pathways that are involved in drug induced toxicity, how drug metabolites might stimulate cellular signaling pathways that are different than the parent drug itself. We have many drugs. We focused on HIV research. There are many drugs that we were the first to

publish their pathways of metabolism and really understand their kinetics in detail and, as part of that, we were always building analytical methods, mostly mass spectrometry based methods around proteomics, metabolomics, including doing really early on work in single cell proteomics and metabolomics.

So for 12 years, I was a professor at Johns Hopkins. I still have a faculty appointment there, and I was also chair of the Department of Pharmacology at Hopkins as well, and prior to that I was associate dean for research.

So now at FDA, I'm leading the Office of the Chief Scientist. We really try to provide FDA-wide leadership, planning, scientific training, and expertise to try to galvanize the translation of applied research and regulatory science in ways that can forward the FDA's mission. We work to stimulate collaboration inside and outside of the agency and of course you know through NCTR this function of doing this cutting edge world leading research around toxicology. So it's really a priority to me to make sure that to the best of my ability that NCTR has all the resources and support that it needs. We certainly have the full support of the Commissioner of FDA who is also very enthusiastic about NCTR and always refers to it very publicly as a real gem at FDA.

So I view my role really to enable all the science and support all the scientists at the agency and advocate for all of our scientists, but certainly I'm working very closely with the NCTR as they're part of our office directly. So again, I'm happy to answer any questions anyone might have, but thanks again for this meeting and being part of this commitment that I know we all have to strengthening and bolstering NCTR.

DR. GANEY: Are there any questions for Dr. Bumpus? Well, let me just say that we appreciate your commitment to NCTR, as well. Thank you for that report and for your comments, and I know your day is very busy. I can only imagine. So we thank you for taking time to come talk to us.

DR. BUMPUS: Thank you, everyone.

DR. GANEY: Next on the agenda is to hear from the Center for Biologics Evaluation and Research.

Agenda Item: FDA Center Perspectives

Center for Biologics Evaluation and Research

DR. ELKINS: My name is Karen Elkins. I'm the associate director for science at CBER, and I'd like to tell you a little bit about what we do at CBER in terms of our regulatory mission and in terms of the research that supports that, and then really getting to the point about

several of the NCTR/CBER collaborations that are supporting our product development activities.

Tucker sort of stole a little bit of the thunder by mentioning several of them early on, so I apologize for duplications, but maybe we'll have a little bit more detail here.

CBER's mandate in the world is to ensure the safety, purity, potency, and effectiveness of biological products. Biological products have a particular definition in law. It's gotten a little fuzzier as science has gotten a little more complicated, but in general, we regulate vaccines, allergenics, blood and blood products, and an ever-growing list of cell, tissue, and gene therapies, all of which of course are intended to treat human diseases.

Another large part of our mandate is to protect the public against emerging infectious diseases, and we have certainly lived that directive plenty in the last couple of years.

Our work is divided among several offices. These are the three offices that are -- four offices -- that are most involved in the direct product review: the Office of Vaccines includes not only obviously vaccines, but also allergenics and live biotherapeutic products. The Office of Blood includes blood components, devices related to blood testing and HIV diagnostics, and then Therapeutics

includes plasma-derived proteins and recombinant derivatives, intravenous immunoglobulins, polyclonal preparations, gene therapies, human tissues, cell products, and xenotransplantation products, which has had a bit of a moment recently.

Those activities in the product divisions are supported by the Office of Biostatistics and Pharmacovigilance, which is not in the direct product review business, but is in the business of all the data analysis that goes along with that.

Our research interests are bulleted here per our strategic report, and they include developing and evaluating technologies and tools that support the evaluation of medical products, particularly the proof of concept and nonclinical phases of product development. We also aim to enhance the validity of clinical trial evaluations and look at innovative statistical, analytical, and modeling approaches to clinical trial design. We have an active research group interested in those aspects.

We strive to proactively address public health challenges in emerging infectious diseases. Again, something we have really lived in spades in the last couple of years. And then generally advance the scientific capabilities to assess novel technologies and innovative

medical products in ways that inform our regulatory oversight and review of those products.

Our research programs are directly aligned with our regulatory purview. They include research in viral bacterial and parasitic vaccines and that can range from basic pathogenesis studies to immune responses, correlates, and specific sub-vaccine constructs and platforms. We have programs in allergenics. We have programs related to the big class of live biotherapeutic products: phage treatments, fecal microbiota transplants, and probiotics that are intended for medical purposes, not as food supplements so much, but for specific medical indications.

We have research programs in CAR-T cells, all the viral gene therapy vectors and CRISPR systems that are becoming an increasingly large part of developing those kinds of vectors, research in polyclonal immunoglobulin treatments and blood substitutes, the vascular biology, pathogen reduction in blood and blood related storage issues, and then our pharmacovigilance group looks at the epidemiology of diseases and both methods and approaches to understand adverse events better.

Our research expertise, again, goes along with that menu. We have a lot of microbiologists. We have very busy and tired virologists, along with parasitologists, bacteriologists, and people who specialize in microbiome

research. We have immunologists, particularly immunologists that are focused on infectious diseases. We have biochemists and molecular biologists, cell and developmental biologists, people interested in tissue engineering and microphysiological systems. We have epidemiologists and those that are expert in meta-analyses of large healthcare databases that are a major component of our research and regulatory activities. We have biostatisticians and bioinformatics specialists, also hard to hire here as everywhere else. And then we have people who are expert in particular applied technologies such as NMR, mass spec, flow cytometry, and next-generation sequencing.

That research expertise is closely aligned with regulatory expertise because I should hasten to point out that our researchers are also regulatory reviewers. Our researchers are assigned the product aspects of regulatory submissions, specifically the chemistry, manufacturing, and control reviews, along with understanding the scientific rationale for products that come to us and any clinical lab based assays that are conducted as part of a clinical trial effort.

I'd like to give you just a few snapshots of the collaborations that are active right now, and they cut across topics such as lipidomics, metabolomics, and

everything related to omics, some structural modeling and bioinformatics projects, projects related to microphysiological systems and airway tissue systems, and then of course projects related to all kinds of toxicology and alternatives to animal testing. Right now we have about 15 collaborative projects that are very active and in the works. So what I'm going to tell you is in various stages of progress.

The first example is one that is relatively new that has to do with our pathogen reduction technology program that is reducing pathogens in the blood supply. This is a collaboration between CD Atreya from CBER and Dr. Sun from NCTR, and CD is studying the ability of 405 nanometer light treatment of blood to reduce pathogens by ex vivo treatment of plasma and stored platelets.

So the question is what does the light do besides get rid of pathogens that are undesirable? Does it leave behind things that are desirable? So NCTR contributes its expertise in metabolomics and has analyzed treated samples for us, and that analysis indicated that the light treatment doesn't harm important things, like platelet activating factors or agonists or prostaglandins. It also has told us that there are increases in hydroxyl fatty acid levels and aldehydes, combined with decreases in antioxidants, and that suggests that the mechanism by which

405 nanometer light reduces pathogens may involve a reactive oxygen species. So this is an example of a collaboration that is informing both a safety aspect of a product in question and a mechanistic aspect of the product in question.

Another act of collaboration is between Marion Major here and Dr. Hong at NCTR and Dr. Mazumder at George Washington in which we are obviously interested in immune responses to SARS-CoV-2 where NCTR has expertise in modeling protein structures. So the goal of this project is to identify amino acid residues and more specifically motifs that are under negative selection pressure and that may be good targets for COVID-19 vaccines because they are invariant. So Dr. Mazumder has analyzed a very large number of isolates, SARS-CoV-2 isolates, to look for invariant motifs and then in the spike sequences specifically, and those will be incorporated into a 3D model by virtue of this collaboration, and the 3D model used to select specific mutations to test by making recombinant pseudo viruses and looking at the impact of those mutations on particle assembly and on virus-receptor interactions. So that project is well along and going well.

Inflammatory toxicology is a major problem for CAR-T cell therapy, and this is the collaboration between

Nirjal Bhattarai and Kelly Mercer. Nirjal is developing a mouse model to study the inflammation that often accompanies CAR-T cell therapy, and NCTR of course is contributing its toxicology expertise. So the idea here is to use the mouse model to look at toxicities that develop during CAR-T cell therapy and to study -- to use that model to study mechanisms that contribute to toxicity and correspondingly develop treatment strategies. The model also might be used simply to assess the next generation of CAR-T cell therapies, which are expected to be even more complex than the current generation.

Evi Struble and Dayton Petibone have had a productive collaboration about microphysiological systems. Evi has been interested in the impact of Zika virus infection on pregnancy and polyclonal antibody treatments that may be used to mitigate the consequences of infection, as well as developing potency assays for those polyclonal antibody treatments, whereas NCTR has expertise in the organoids and microphysiological systems. So the goal is to develop an in vitro approach to study the interactions between Zika virus and polyclonal antibodies and this is particularly focusing on the development of semipermeable placental membrane structures in order to assess the infection, and then to determine whether the infection can be modulated by antibody treatment.

And then a project that is very new, haven't gotten very far, but that is exciting so I thought I'd mention it, is between Chava Kimchi-Safarty and Richard Beger at NCTR. Chava has long been interested in the interactions between human coagulation-related proteins, which we regulated, and SARS-CoV-2, and coagulation problems are a big feature of COVID-19 infection, particularly with different genetic variants. So NCTR has not only the expertise in multiomic analyses and profiling, but it had access to a large panel of plasma samples from SARS-CoV-2 patients who have different disease severities. So the omics analyses of those plasma samples includes looking at a variety of proteins, autoantibodies, microRNAs, lipids, metabolomics, vitamin D, and glycan, and so all of that information will be evaluated in this collaborative project, the search for pathways that are associated with anti-COVID-19 responses and biomarkers as well as pathways that may underlie the different severities of disease as well as the clotting abnormalities in these patients.

So I hope that gives you a whirlwind snapshot of some of the activities we have going on. The future possibilities are more of the same. Obviously all product toxicity-related topics are of interest. We have relatively limited expertise in toxicology, per se,

including reproductive toxicology, and an awful lot of biological products are either used during pregnancy or are envisioned would like to be used during pregnancy. So that's a fruitful area for us to work together.

All kinds of omics needs as much brainpower and bioinformatic power as we can assemble between us all, and I think one ongoing area of collaborative interest will be in vitro cell culture alternatives for animal use, not just for toxicology and safety related purposes, but also to understand efficacy and mechanism of action.

We hope that we can continue to mutually leverage our complementary expertise to support the evaluation of the products that we regulate and particularly aspects related to product safety but that set of examples demonstrates, I think the opportunities for understanding mechanisms and biology is also ripe.

Thanks very much, and I'm happy to answer any questions.

DR. GANEY: Thank you for that informative presentation, particularly the description of the projects and the illustration of the contribution of people from CBER versus NCTR. That was really helpful.

Dr. Lanza, do you have a question?

DR. LANZA: Yes, I do. With regard to the CAR-T cells, essentially this cytokine release syndrome or really

a form of cytokine storm is inherent in the mechanism of how those and other T cell related immunotherapies work. So I'm a little -- I wonder if you could clarify how you're going to separate what's toxic from what's mechanism of action.

DR. ELKINS: So, that would be a question better directed to Nirjal than to me, because it's his area of expertise, but my understanding is that the use of the model which is the SCID/Beige transfer model is intended to allow blocking of individual components of the inflammatory pathways so that you can understand more about the interactions of the multi-components. I'm not sure if that answers your question, but that's the general idea, I think.

DR. GANEY: Any other questions for Dr. Elkins? All right, thank you very much for your time.

DR. ELKINS: Thank you, and I'll let you hear from our colleagues at CDER.

DR. GANEY: Okay, CDER, you are up next.

Agenda Item: Center for Drug Evaluation and Research

DR. CLINGMAN-HENRY: Good afternoon. My name is Chekesha Clingman-Henry, and I am the acting deputy director for science for the CDER Office of Translational Sciences within CDER/FDA. I am somewhat new to this

position, being in this role for about two months now. Prior to that, I have had a number of roles at CDER as well as I'm in the Office of the Commissioner, working to facilitate scientific research internally amongst CDER and other centers, as well as externally with some of our stakeholders in industry and academia, as well as consortia. So I look forward to speaking with you today.

First, I want to share perspectives on regulatory science research activities at CDER, and the center's efforts to assess the impact of regulatory science research on advancing CDER's public health mission. I also want to highlight some recent scientific collaborations with NCTR and discuss opportunities for engagement.

CDER's regulatory science and research activities are aimed at speeding the development of safe and effective drugs. CDER's intramural and extramural research investments support the creation of new tools, methods, and analytical approaches that enhance the evaluation of new drug products. These efforts also support development of new processes and technologies to evaluate the quality of drugs. In addition, our investments support development of information systems and computational tools to help the center promptly identify issues with regulated products.

The CDER Research Governance Council was created in 2017 to provide oversight of CDER's research program.

The RGC was charged with establishing broad goals and objectives for CDER's research program and to advise on the execution of CDER's research investment portfolio. The RGC oversees central research functions for CDER, including the conduct of research portfolio evaluations, development of research outcome metrics, as well. Additionally, the RGC helps to coordinate scientific interactions among CDER offices and other FDA Centers.

The RGC developed CDER's research goals and objectives as a broad framework to encompass all of CDER's research activities and align with our core mission requirements. There are five research goals which I will discuss on subsequent slides. Objectives pertaining to more specific research activities are aligned with each goal.

Within CDER's project tracking system, we have tracked projects by the research goal and objective they aim to address, as well as research outcomes and other metrics, such as the associated budget and relevant training programs including ORISE fellowship.

As mentioned, CDER's research goals are broad but share a common theme. A product should be designed to produce outcomes with regulatory impact, to inform development and regulation of the products we regulate. Goal 1, develop and improve scientific approaches that aid

in developing new drugs or evaluating their premarket safety and efficacy. This goal encompasses advancing clinical study methods. For example, statistical approaches to complex trial design and analyses, as well as exploring approaches to incorporate patient experience data and regulatory decision-making. Other objectives cover the development and evaluation of predictive models, biomarkers, and other drug development tools to advance product development and the evaluation of drug efficacy and safety.

Goal 2 relates to improvements in scientific approaches to enhance the safety of marketed drugs. The objectives associated with this goal target the development and execution of tools and data sources for monitoring safety. Other objectives involve assessing the accuracy and effectiveness of product labeling, product description promotion, and other forms of communication relevant to marketed drugs.

Goal 3, improve product manufacturing, testing, and surveillance to help ensure availability of high-quality drugs. The objectives here focus on advancing science-based quality standards and manufacturing processes to assure product quality, safety, and efficacy. They also involve development of novel tools and methods to monitor and assess quality of drugs.

Goal 4 focuses on activities to facilitate development and review of generic drugs and biosimilars. This includes development of in vitro and in vivo as well as in silico approaches to improve the demonstration of similarity for biosimilars. The objectives associated with this goal involve activities to improve quantitative tools and methodologies for evaluating bioequivalence of generic drugs.

Our final goal highlights CDER's need to maintain scientific readiness to address emerging public health threats and regulatory integration of emerging technologies, and also the ability to facilitate stakeholder adoption of novel approaches to drug development.

So this graphic just really gives an overview of CDER's research landscape. Research efforts in support of CDER's mission, like other product centers, are shaped by many factors. Research drivers include congressional initiatives such as 21st Century Cures Act, the domestic drug manufacturing, supplemental appropriations to address the public health crisis such as COVID-19, and the opioid overdose epidemic. Priorities aligned with user fee agreements are significant drivers, as well. Research allocations may also be determined by reports of adverse events associated with approved drugs that require follow-

up studies or issues associated with pending market applications. Research needs also may arise from knowledge gaps identified from review of regulatory submissions. These drivers inform the development of research concepts and the design of targeted research proposals focused on priority areas.

Next, appropriate resources are identified to support the conduct of the research. This includes identifying funding sources, equipment, and needed expertise, whether internal to CDER or through collaborations with other centers or partners external to FDA. Mechanisms of engagement are important as well. For example, will we need to enter into research collaboration agreements or CRADAs or are grants and public/private partnerships primed to fulfill our research objectives?

It is important that the results of CDER's research in support of our goals are disseminated appropriately to inform further research and new processes and tools to advance development of regulatory review. We must assess the impact of our research outcomes to ensure that efforts are helping to fulfill our public health mission in an efficient manner.

The RGC developed two broad categories of research outcome measures. They are communications outcomes and regulatory outcomes. Communication outcomes

document how the research results are being shared to appropriate stakeholders, and these include presentations internal to FDA, as well as external presentations at conferences and workshops. This also includes journal articles, white papers, and technical reports.

Regulatory outcomes link research results to development of regulatory tools such as new standards, drug development tools, and reviewer tools. Examples of regulatory outcomes in the form of regulatory actions may include activities that support guidance development, product recall, or product labeling.

As mentioned previously, CDER goals and objectives are used to track project plans and/or outcomes. This slide shows a distribution of CDER research projects reported for FY22 data call according to CDER's research goal. Over 800 CDER-funded projects were reported in FY22. These projects are self-reported by our research scientists. Most of the projects reported were aligned with goals 1, 2, and 4, which aim to advance scientific approaches that support development and evaluation of premarket safety and efficacy, as well as the safety of marketed drugs and development and review of generics and biosimilars. All three goals are focus areas for a number of CDER/NCTR collaborations, and I will discuss some examples of these in later slides.

Project outcomes that were reported pertain to advancing the design, analysis, and conduct of clinical trials, new tools, and methods to accelerate development and evaluation of new drug products, as well as approaches and techniques to enhance safety of marketed drugs and analytical methods to assess product quality.

In support of CDER's efforts to communicate outcomes of CDER's science and research efforts to public stakeholders, the center has been posting impact stories and spotlight on science articles and other content on the FDA regulatory science webpage. This site contains a lot of great information on how CDER's research activities directly support our public health mission. I encourage you to take a look at these. Some of the exciting work that CDER is doing with NCTR has also been featured in these publications.

Now I want to shift gears and highlight some examples of ongoing CDER/NCTR research collaborations that are in various stages of progression but that are also poised to have a significant impact on drug development and regulatory decision-making.

This project is a collaboration between CDER scientists in the Office of Biostatistics who are working closely with NCTR scientists including Dr. Dong Wang, and they're working on a number of efforts, including the

development of statistical tools for assessing next generation sequencing technology used to evaluate biomarkers and precision medicine application. This is a critical area of research in oncology and other disease areas. Multiple factors including the type of NGS platform and application settings can affect the biomarker performance. NCTR biostatisticians are applying statistical approaches to project the performance profiles of biomarkers under conditions of various technologies and settings. The results of this study will provide tools to aid reviewers' evaluations of biomarkers and precision medicine applications derived from deep sequencing applications.

This project is a collaboration between CDER and also NCTR scientist Dr. Heflich. NCTR is conducting studies that are increasing CDER's understanding of the mutagenicity of N-nitrosamine drug impurities. Nitrosamine drug impurities pose unique regulatory challenges as they can typically form during drug synthesis and possibly from the drug substance itself. NCTR scientists are developing methods to optimize mutagenicity assays like the Ames test for detecting mutagenicity of nitrosamines and are evaluating the utility of in vitro mammalian cell assays for testing genotoxicity of these compounds.

Data generated from this study will enhance development of QSAR models for predicting mutagenicity and may inform the development of improved bacterial and in vitro mammalian assays for use for risk assessment of nitrosamines.

Next slide, please. This is a collaboration between NCTR and CDER, and it is supporting CDER's efforts to address the COVID-19 pandemic, specifically efforts that will inform at the molecular level an understanding of differences in severity of infection and disease and patient response to treatment. This project is using systems biology omics to analyze plasma from COVID-19 patients to help characterize the difference in symptom responses between asymptomatic patients and patients with mild symptoms versus patients with severe and/or critical responses to SARS-CoV-2 infection. The results may inform predictive factors related to differential outcomes among these patients and also may aid in the identification of new therapeutic targets for COVID-19.

Another project addressing a critical public health need, that is the opioids crisis, and this study is using big data analytics and AI to evaluate FAERS data, electronic health records, and other data sources to enable the identification of sex differences in prescription opioid use associated with cardiovascular disease. The

outcomes of this project may aid in the evaluation of postmarket safety of opioid products, providing insight regarding which opioids and concomitant use of opioids with other prescription drugs may potentially increase cardiac risk in women.

This last example highlights a recently completed CDER/NCTR collaboration to improve product manufacturing by advancing methods to assure product quality and safety. B. cepacia complex contamination has been the cause of recalls for both sterile and nonsterile pharmaceutical products. These microorganisms have been implicated to cause severe infection and death in susceptible individuals. Researchers at NCTR as well as CDER conducted a comparison of various test methods for assessing BCC contamination, which contributed to the adoption of a U.S. Pharmacopeia chapter entitled Microbiological Examination of Nonsterile Products Tests of BCC. And it also contributed to an FDA advisory to drug manufacturers about contamination risks.

The previous examples highlight the impactful collaborative work between CDER and NCTR to address challenges to drug development and review, and ultimately advancing public health by assuring the safety, quality, and efficacy of regulated products. These, as well as others listed here, represent areas of continued opportunity for engagement between CDER and NCTR, certainly

addressing the opioids crisis is among -- is an ongoing research priority for FDA and CDER as well as advancing toxicological studies to assess drug impurities and biological product constituents.

Studies that further the center's understanding of factors that contribute to mutagenicity of nitrosamine drug impurities is also a critical need. In addition, activities to inform the development and adoption of alternative methods to traditional toxicity and efficacy testing and approaches to assessing the utility of machine learning and bioinformatic methodologies to predict adverse events are of interest, as well.

So I just want to really close to reiterate that CDER is extremely dedicated to strengthening our collaborative relationship with NCTR and enhancing our ability to leverage resources and expertise to support FDA's mission. Streamlining the process for CDER and NCTR scientific engagement is a priority for the CDER Research Governance Council, and we are looking forward to working with NCTR on this. An ideal process should include clear articulation of CDER research goals, enhance collaboration between our two centers in the early phases of project planning with specific research targets to better understand and plan resources for ongoing versus term projects.

Also we want to continue the exchange of expertise during the lifecycle of the project and ensure that we are capturing salient milestones and research outcomes and working collaboratively to translate these outcomes to research impact.

This concludes my presentation, I believe. Thank you.

DR. GANEY: Thank you very much for that informative presentation. Are there questions for CDER from anyone in the group?

DR. COSENZA: I have one question. This is Mary Ellen Cosenza. I just note that the CBER presentation discussed the collaboration on the CAR-T cells and cytokine release syndrome, and I know that there are many products that are regulated by CDER that try to work in similar ways, some of the new biospecifics and more advanced antibodies. So I just wondered whether that might also be an area of interest to CDER to collaborate on that project as well. Just really a comment.

DR. CLINGMAN-HENRY: Sure. I agree, absolutely. As I was looking at the CBER presentation, certainly, and don't quote me, but I believe that there is some sort of multiple center collaboration on some of those efforts, but certainly I think that's an important issue that we would want to continue to support.

DR. GANEY: Alex, did you have a question?

DR. TROPSHA: Yes, quickly, first kind of logistics, I don't think this presentation is in the books. I'm not sure, but I was looking for it and didn't find it. So maybe, Donna, you can address this because I think it's important for us to have.

My question is on the dynamics of the collaboration between CDER and NCTR, I'm wondering if you view NCTR as a resource that you go to when you have a problem or a challenge, or it's a two-way street anyway. For instance, Weida's group has developed a new approach to document review and they're looking for customers and they could contact us. Could you comment on how projects are initiated?

DR. CLINGMAN-HENRY: Sure. Very good question. So, currently the process, certainly we accept concept papers, so there's two ways that things are currently done at the moment. There are sort of center-directed project proposals and interests that are communicated to NCTR, as well as we also have what we call our NCTR-initiated project prioritization and review process. So those are the current ways.

I think what certainly we've had great success both ways. There's been synergy that has really led to the development of meaningful outcomes given both processes. I

think moving forward, but we also do recognize that there are some challenges or opportunities to improve this overall process.

I think what I'm hearing from CDER scientists is certainly as well as from NCTR is that there -- it would be great to have sort of more enhanced communications or early on and collaborative engagement to further refine different protocols or in concepts of protocols that come over to CDER for consideration. I think that would ensure that the projects are really targeting our focus areas and that we're having sort of a mutual approach to conducting that research and then also sharing those outcomes.

DR. GANEY: Thank you, Dr. Clingman-Henry from CDER. Now we will hear from the Center for Devices and Radiological Health.

Agenda Item: Center for Devices and Radiological Health

DR. EPPIHIMER: Thank you, Patti. I am Mike Eppihimer. I am the division director for Biology, Chemistry, and Materials Sciences, which resides within the Office of Science and Engineering Labs, which is the research arm of CDRH. My talk is going to be a little different today. It's going to kind of tell us how we operate, some of where and how we develop our research programs, and how we identify our products. We do produce

a product in CDRH; while it's free and publicly distributed, we do view what we produce as a product, because we've undergone significant transformation over the last couple of years and we're kind of going to explain that.

So CDRH is quite unique in what we conduct; about 22,000 premarket submissions a year. Many of the technical consults actually come to the Office of Science and Engineering Labs.

What's unique about CDRH is that we oversee the regulation of 238,000 medical device types, which are very unique in nature. So obviously we can't work on every device type. So it's extremely important in our research to identify which area we should work in that will have the greatest impact.

OSEL, we have approximately 179 staff and an equal number of visiting scientists and research fellows. We conduct more than 3,000 premarket reviews where we assist the Office of Product Evaluation and Quality. We publish about 400 manuscripts a year and we have 20 research programs which encompass approximately 140 research projects. The office, one thing that I want to mention is the office, like I said, has undergone significant transformation in how we operate and are focused with research. We have moved away from a PI-

centric kind of academic model which publications were kind of our currency and our product to something, to a new product that we call the regulatory science tool. I'll explain the difference a little later in the talk about that we don't view the publication as the regulatory science tool and an explanation of why.

So the goal of the research in CDRH is to have an impact on evaluating the safety and efficacy of medical devices, and where we view where we can have an impact is along the entire product lifecycle in medical devices through all the way through early development in the design of products, testing of products, replacement for animals, those things that can ultimately support, enable a manufacturer to use that will facilitate the review of their submission. Hopefully with the outcome of fewer deficiencies that will provide access to patients in a more accelerated manner.

So regulatory science tools. Where do we feel we're applying? Regulatory science tools do not replace FDA recognized standards. The tools represent a peer-reviewed resource for companies for them to use where standards don't exist, and these tools can be computational models, they can be risk analysis tools, in vitro models. It's phantoms, those sorts of things.

Where we see regulatory science tools are, they reduce the need for device developers to design the actual test methods themselves, and it allows the device manufacturers to focus their limited resources on actually on how the product works. This is extremely important for many small companies who have very limited resources and are looking to get their first product to market. So we view these tools -- they represent an important contribution to manufacturers in reducing the risk during product development.

In terms of communicating our regulatory science tools, we make them publicly available. We have a catalogue that is part of our website of which as they are developed and qualified, they are placed on our tool catalogue.

So where we're moving our tool catalogue and regulatory science tools. So we're expanding the product catalogue. We're actually making it the -- we are creating a library that is the go-to place for medical device manufacturers, and we are expanding the regulatory science tool kind of its use. Instead of simply in the past it was a publication that somebody would read and try to implement it within their own hands, which in many cases is very difficult because of a lack of details that are often provided, our RSTs with each of our regulatory science

tools, we include what we would say owner manuals or directions for use. These are details that enable product manufacturers to be able to -- it almost makes it turnkey for them. They don't need to spend time further developing the tool within their own hands and the tool is qualified to support a defined context of use. So that enables manufacturers to really know how this tool, where this tool is going to be applied.

We look at this as we're working in a precompetitive space. So these things are made publicly available and these methodologies have an intrinsic and tangible value. So the program is in place currently. We have been working for the last few years to put it in place. We have approximately 120 regulatory science tools across many research programs which have produced them.

What's also important for us is that we demonstrate that the tools that we did develop, that they're actually providing -- having an impact and providing value. So as a key indicator of the value of our tools, we're measuring their impact, their use in premarket submissions. For an example, we are able to go in and measure the mentions and use of one of our regulatory science tools so that we can assess, kind of come up with a metric for impact.

For example, we have one regulatory science tool. It's called the virtual family of tools. We've recorded that it's been used 672 times in premarket submissions.

How do we develop our research programs in OSEL? We really, we focus, both the office director and myself, we both came to FDA from decades of working in the medical device industry. So our approach then is very disciplined. When we think about our developing our research programs and what we should work on, we really utilize stakeholder input and a desire for execution excellence, because in the past, we had as one member said, when do you know that you have really too many research projects for the resources you have?

We were hit with that dilemma several years ago when we realized just in my division alone I had 120 research projects from staff, all working a little bit and the projects kind of going a little bit longer than they should have. So through this mechanism, we identified key priority areas that were really must-haves, and we now are operating with between 30 and 40 actual research projects. So we're able to accelerate the development of our tools much greater because we have a critical mass for the number of projects.

So how do we develop a regulatory science tool? The concept, the idea, for a program can come many ways.

Our staff review submission trends. We look at real-world evidence. There's regulatory, environmental, legislative changes, that require -- that may be the nidus for an idea for a research program. However, before in the development of that program and assessing whether there's actually a need, we have a rigorous stakeholder input from both internal and external stakeholders where we interview, we gather feedback, we understand the needs of the customer, in many cases the medical device manufacturer.

We then look at the data and we identify what are the gaps that are out there and what are opportunities that we believe CDRH should pursue, because we can't pursue all opportunities. We look at what the tool requirements would be, and then we extensively -- then, once that is decided, we develop our program charter. We use project management concepts to essentially prioritize the gaps, develop detailed project plans which include program, clear program goals, deliverables, and milestones, of which we have evaluated resources and timelines against.

And then once this is approved, we maintain those project management principles. We track them electronically with key performance indicators and metrics to demonstrate that we're remaining on time. These are often, these plans undergo risk analysis and mitigation strategies to ensure success.

Our timelines of developing tools now, we are currently developing these tools from beginning to end in approximately two years or less now. That's kind of been the mandate so that we have a continual stream of regulatory science tools coming out.

Once the tool is developed from the scientist, it undergoes qualification by a technical review board that we have within the office, so that we're along with then the publication, the project team develops the user manual and presents it to management for review, and once that is done, we require that they have a communication strategy put in place. So that is the dissemination of the information and any training materials that would need to go with it. So we're currently using webinars, videos, that we attach to the regulatory science tools so that we get quick adoption, and we really minimize the complexity for somebody to actually run it.

One thing I do want to say is that all of this is done under the quality management system that's being established by FDA, which is ISO 9001, which will be accredited to ISO 9001. So we have procedures in place, both in management review of all of this.

So here is a case example. We developed the Sterility and Infection Control Program within my division. We utilize stakeholder input to define the key priorities

that would require future regulatory science tools. So how do we gain our feedback?

We use trade organizations. They will gather groups of sterilization manufacturers and companies. We use other mechanisms. We talk to CDRH reviewers. We talk to the external companies. And we really -- we get a very deep customer needs of which we're analyzing. When we did this for the Sterility and Infection Control Program, a lot of things come out, and if we didn't prioritize and kind of look for high impact things, we'd be working on, the project list would or program list would grow immensely.

So essentially when we performed this analysis, what came out of it was the two key areas was alternatives to ethylene oxide. Right now there's a critical need and a push for manufacturers to move away from ethylene oxide which is the primary mode of sterilization, and the ability to bring alternatives forward is extremely difficult. It's very burdensome from a regulatory viewpoint. So this program identified four key gaps, one which is actually microbiological focus, but the other two are actually -- one is around materials compatibility and the other is actually computational modeling, being able to model penetration of these novel sterilants, which is ultimately a determinant for whether it can be adopted or be utilized by a manufacturer.

So all of our teams are multidisciplinary in nature. This team in particular has again, when you think sterility and infection control, they have microbiologists. But they also have analytical chemists, toxicologists, and computational modelers. So we also came out with device-related infections. Again, very broad topic and so that's however then what we do is we narrow down what the focus is of, say, device-related infections.

For our device-related infections, what came out of it were really three areas. One is endoscope drying validation. So, how dry is dry? If endoscopes are not dry, the moisture can lead to propagation of biofilms and other bacterial growth. So there's currently no methodology or standard around how to appropriately evaluate drying and how dry is dry?

Also cleaning endpoints. Right now cleaning endpoints are not based on, say, risk of the device. So the manufacturers gave us an indication of could we develop kind of a Spaulding type classification, something like a Spaulding classification based on risk for devices.

Another was biofilms. One area that's critically important and especially on devices, many devices when we look are just not eluting antibacterial, say, antibiotics, but many devices are using surface treatments,

technologies, coating technologies, to possibly disrupt or prevent biofilm adhesion.

These are very innovative technologies, and the burden for proof to get approved is very high. So one of the areas that manufacturers have indicated to us is where can we develop our regulatory science tools that will help facilitate biofilm product claims? Also, evaluating antimicrobial technologies and really -- so in CDRH, there are no standardized endpoints and methods for determining biofilm removal. So all of these were key areas that were identified and projects that were created.

So that process that I took you through, this is what -- these are 20 programs that we have that have all undergone stakeholder and prioritization using our prioritization process and criteria. What I have here in red are programs with efforts where NCTR could contribute. So these are areas that NCTR would likely have expertise in that could contribute to projects that we're working on.

So really next steps.

DR. GANEY: Hey, Mike, I'm going to interrupt you just to tell you that you have two minutes.

DR. EPPIHIMER: This is the last slide. As I said, all of our regulatory science programs have undergone stakeholder and prioritization. So all of the gaps that have been -- so we make our, the gaps and efforts that we

are working on, we make them publicly available. They are programs; we have webpages for all our programs that identify the current gaps out there, and the projects that we're looking for people to work with us on to develop these tools.

We're also doing a lot -- so how we fund our projects a lot of times through either intramural and extramural funding. However, we have a goal in OSEL is that 50 percent of our gaps are being worked on by other people, because we don't have the resources to develop tools for 238,000 products. So the Sterility and Infection Control Program is kind of what I set as a gold standard for that group has established four major research, five-year research collaborations. Three with major device manufacturers who themselves are dedicating multiple -- who are dedicating, they're not providing us funding, but with this collaboration, they are actually providing people and materials for this active collaboration.

One of the manufacturers is providing us -- as part of the research collaboration -- is providing up to four fulltime staff to develop these tools. So we're seeing, we've communicated our needs and we've engaged with these organizations and companies and are finding that they do want to work with us to develop these tools.

So, in the end, advancing the regulatory science tools, it's a team sport. So we're looking at active participation by all stakeholders, whether it's internal or external, and we're starting to see people -- we are starting to move the needle dramatically in this area.

Thank you. Any questions?

DR. GANEY: Thank you very much. It looks like Greg has his hand raised. We're kind of crunched on time, Greg, so if you can be --

DR. LANZA: One question. It's outside regulatory devices, but working in imaging, things are changing greatly with AI, and very soon AI-based quantitative metrics are going to be able to do the image interpretation for initial diagnosis and longitudinal patient management, and I am wondering what are you doing in this area, because this is not some fantasy. This is maybe just a few years off the road, and in part of that, it involves actually using data that's being generated on scanners broadly, both within the United States and beyond.

DR. EPPIHIMER: Yes, so we actually have a very large active program in that. It's likely it's those efforts are kind of between two programs, one of which we have the digital pathology program. So they are developing the tools to evaluate the adequateness of algorithms that are being used to score and to identify abnormalities not

only in tissue but were also then from, say, CAT scans, MRIs, what is the machine learning algorithms that are ultimately going to be used from a diagnosis standpoint? So those are two very large programs within one of our divisions. So we are very active in that area. We have a very large artificial intelligence program as well, mixed learning programs.

DR. LANZA: I am just hoping that you've got the horses or you can find the horses to deal with the longitudinal management issues, because this is going to be impactful and a lot of people sometimes look at what comes out of the box as the truth, and it may not be. There's going to be a lot happening quickly in this area. So I just wanted to get it on the table so that you get the funding you need to really do this. It's going to be across modalities.

DR. EPPIHIMER: We are investing heavily in that area. We have long-term funding. So the way -- we don't operate on a per grant basis anymore. The way we operate our budgets is I may -- the way I handle my budget now is not simply on a year-to-year basis, hoping that I get funding, a grant proposal renewed, and then the project goes long and you can't finish it. Right now, within my division, I'm planning out almost five years. I have long-term budget planning of how I manage this year to year and

how I'm going out and obtaining either new funding or managing internal funding.

So I don't, I bring a very much -- we have brought so much project management into all of the projects. I have as part of my team itself, we have a lot of -- I have multiple certified PMPs that really work with the teams and myself in a lot of this planning. So longitudinally or long term, we have posed ourselves for success.

DR. GANEY: Okay, I know that, Alex, you have your hand raised, but I'm going to ask you to communicate with Mike offline, because I feel like we need to adhere to the schedule. So I'm going to terminate this part of the meeting.

Thank you very much, Mike, for that informative presentation. We will reconvene at 2 p.m. Eastern or 1 p.m. Central. We'll see you all then.

(Luncheon Break.)

AFTERNOON SESSION

Agenda Item: Public Session

DR. MENDRICK: I'm Donna Mendrick. Again, I'm the designated federal official for this meeting, and we've had one request for a public comment, from the Physicians Committee for Responsible Medicine, and I'm hoping his name correctly. It's Joseph Manuppello.

DR. MANUPPELLO: That's correct. So, I am Joe Manuppello, with the Physicians Committee for Responsible Medicine. PCRM is a nonprofit organization advocating for efficient, effective, and ethical medical practice, nutrition, and research.

My premeeting written comments are brief, and in the last half-hour I've been busily responding to the exciting presentations. PCRM generally supports congressional funding for the types of activities described this morning. I was impressed by NCTR's emphasis on emerging technologies in its 2021 annual report, and that emphasis continues here, and it's good to see that.

However, in its fiscal year 2024 justification of appropriations, FDA highlights the need for comparative assessments between traditional animal-based testing and emerging technologies to ensure the reliability of new nonanimal methods for product development and regulatory

decision-making, to support its Predictive Toxicology Roadmap, and advance alternative methods specifically.

Such methods can both enhance predictive capabilities and reduce animal use, but we are concerned that FDA may use these funds to conduct new animal testing. Due to the limitations of animal-based testing, which include high variability in test results, to which Dr. Tong alluded this morning, nonanimal methods should be compared to effects in humans whenever possible. The ultimate goal is to develop alternative methods that not only match but also surpass predictive ability of animal models, providing more accurate, faster, and cost-effective results.

A popular success story is to find approaches for skin sensitization which combine nonanimal methods with computer models. In this case, a wealth of human data were available and compared to existing data from local lymph node assays in mice. The defined approaches were more predictive of effects in humans. When adequate human data are not available, comparing nonanimal methods to existing data from traditional animal-based testing is consistent with the goal of reducing animal use. PCRM urges FDA to reconsider the approach described in its justification and to prioritize a strategy that avoids conducting new animal tests using additional animals.

Regarding that 2021 annual report, we are also concerned by ongoing projects in the Division of Biochemical Toxicology that included studies of nicotine and cannabidiol in rats. Due to the limited information available on these projects we were unable to assess the division's rationale for conducting new studies on substances for which toxicity in animals has already been evaluated extensively.

To prevent duplicative testing, PCRM recommends that NCTR publicize its research proposals prior to initiating them. The National Toxicology Program in the past has provided such materials for its Board of Scientific Counselors meetings ahead of time and solicited public comments, and we'd encourage NCTR to consider a similar approach for its SAB.

To measure progress toward achieving FDA's PTR goals, PCRM requests that NCTR track its animal use and discuss it in its annual report and at its SAB. By adopting such transparent practices FDA and NCTR can reduce animal use while better protecting public health.

I'd like to go off-script a little bit here, because I was very struck by a story that Dr. Tong recounted about a project to organize FDA's CDER guidance. I've done, over the past couple of years, I've reviewed a large number of FDA reviews of new drug applications and

published two articles in Regulatory Toxicology and Pharmacology about them, and the one clear lesson is that clear guidance would be -- would just be a big help. There was, with acute toxicity for example, there is still available a 1996 guidance, single-dose acute toxicity tests, that conflicts with the current guidance from ICH, which FDA signed onto, so we have these two conflicting guidance documents available, and that can only lead to confusion for the regulatory community and ultimately more animals being used.

I hurriedly emailed my department director, and we'd love to help with this sort of thing. We've been considering offering to help with new supplementary guidance, but these sorts of efforts as well are very interesting to us, and I'm sure to many of your stakeholders who all want better protection for public health.

I think that's a good place to close. Thank you.

DR. MENDRICK: Thank you very much for your comments.

DR. GANEY: Dr. Patri was originally scheduled to talk to us tomorrow, but he has a conflict, so he will be presenting today on the NanoCore, correct?

Agenda Item: Overview of Research Activities, NanoCore

DR. PATRI: Yes, thank you very much. Thank you, Donna.

Good afternoon. My name is Anil Patri, and I serve as the director of NanoCore at NCTR, in part of the Office of Scientific Coordination. And I would like to provide a brief synopsis of NanoCore research since my last presentation to SAB some five years ago and showcase some of the research progress and projects and future scope of work, and I appreciate feedback from the advisory board on the NanoCore, especially Dr. Greg Lanza has been very supportive in providing guidance from SAB. Thank you.

Standard disclaimers apply to this presentation, which reflect my views and do not necessarily reflect those of FDA.

NanoCore currently has seven scientists, two support staff, and two ORISE postdocs. We have a few vacant positions we are looking to fill.

The mission of the NanoCore remains the same from the beginning. It is to support nanotechnology research at FDA, maintain advanced instrumentation and expertise, and conduct collaborative research to advance to advance our understanding of these complex nanomaterials. For a small group, we cannot take on too many projects, so we strategically kept our focus to two areas, conducting high-value research to answer specific FDA questions; and

standards development, both of which require expertise to understand the nuanced complexity with nanomaterial and conduct high-quality reproducible work that withstands the scrutiny of the subject matter experts.

The knowledge gained from these regulatory science research is utilized for capacity building both within FDA and elsewhere with other regulatory agencies, and this has been very useful for reviewers and scientists at FDA. We also extended, as I mentioned, this training to other regulatory agencies, through multiple avenues, both in North America, Europe, and Asia.

NanoCore maintains significant collaboration in terms of outreach, as a core facility. We support protocols from NCTR research divisions, the details of which you will hear from the division presentations. We have collaborations with FDA regulatory centers, and through the nanotechnology task force that I chair we engage within the agency or intra-agency activities. We closely work with NCI, the National Cancer Institute, to learn about emerging technologies for cancer therapeutics that utilize nanomaterial and with the NIST, the National Institute of Standards and Technology, for standards development.

The National Toxicology Program supported the standards development work, and we are working with them on imaging topics related to micro and nanoplastics.

Our interagency activities are coordinated through a formal interaction through the National Nanotechnology Initiative. You may be aware of that. This is part of the Office of Science and Technology Policy, and the NSET subcommittee and the NEHI subcommittee within the NNI. Those are composed of more than 20 agencies. We meet every month to coordinate anything related to nano.

We interface with other regulatory agencies through the Global Coalition for Regulatory Science Research that Dr. Tucker Patterson alluded to during his opening remarks. We just had the global summit last year on nanotechnology, cosponsored by the Singapore Food Agency.

Through these interactions, we share information with other regulatory agencies and identify knowledge gaps to take up high-value research at NanoCore. In the next few slides I will showcase recent completed projects that we have conducted.

This slide summarizes the recent completed study on liposomal doxorubicin. As many of you know, this is a product that has been approved for clinical use in 1995, with subsequent approval of multiple generics in recent

years. There were literature reports in 2016 that challenged the bioequivalence of generic liposomal doxorubicin. There were publications on preclinical and retrospective clinical evaluation that showed that a generic liposomal doxorubicin product is less efficacious compared to the reference listed drug, which is Doxil.

This prompted us to collaborate with CDER Office of Generic Drugs to take up this research project with an aim to comprehensively characterize multiple lots of liposomal doxorubicin from multiple vendors and conduct an in vivo efficacy study in a tumor-bearing mouse model for bioequivalence. It's a xenograft model.

This is quite challenging, as companies do not produce these multiple lots at the same time, so it took us a few years to acquire these lots and complete the study, both from a characterization standpoint, to find if there are any differences, but also to conduct the animal studies.

An overall conclusion from all the characterization studies we have conducted is that while there were minor differences between lots and between manufacturers, these differences were not significant. We conducted multiple in vivo studies to initially conduct dose range-finding studies followed by efficacy studies. Tumor sizes were monitored with calipers and ultrasound, so

all these results from that you can see, just a summary graph on the right, that shows that there were no significant differences from efficacy.

The results from this study refute the published work, and we found that both generic and RLD have similar antitumor efficacy in an ovarian xenograft model. Again, this is funded by the Center for Drugs.

Another project is on nano silver. As you all know, nano silver is used in consumer products for its antimicrobial activity and is a topic of extensive investigation and publications. The use of nano silver in feminine hygiene products has increased. However exposure, toxicity, and biodistribution in reproductive tissues are limited.

In this study, funded by the Office of Women's Health, we investigated dozens of feminine hygiene products for presence of silver and conducted biodistribution and toxicity upon exposure to vaginal tract in a rodent model. Our investigation included tampons, sanitary napkins, wipes, towels, gels, washes, for the presence of silver. This is a physical chemical characterization. Out of the 30 products we tested, around 14 products contained silver, either in colloidal form or ionic form.

Animals were exposed to silver either as an ionic silver, colloidal silver, a gel product that contains

silver nanomaterial on a tampon or a silver nano wire, along with all appropriate controls. The major conclusion from this in vivo study is there is limited persistence of the administered dose of silver upon acute exposure, with no microscopic signs of tissue toxicity. Of the 10, 15 percent of the silver we were able to recover, over 85 to 90 percent of silver is retained in the vaginal tract. So no distant distribution and toxicity observed from this study.

Standards setting is the foundation for regulation in support of FDA mission. This is an area, as I mentioned, we can bring our network and leadership to bear that will significantly impact, has significant impact for FDA and industry. This is funded by the National Toxicology Program. We collaborate with FDA Centers, with other government agencies, especially with the National Cancer Institute and NIST, standards development organizations globally, with joint research center European and Asian regulatory agencies.

Here is a summary, a list, of achievements from the NanoCore. The list of documentary standards we developed from extensive work in the last four or five years. Most of these are published in the last two to three years. There were seven international standards that came out of this work, and as you can imagine, this is a

significant output, most of them published, again, within the last three years.

As you can appreciate, this is a significant accomplishment given the complexity in developing reproducible methods with nanomaterial and come up with a consensus from subject matter experts to finalize these standards. I applaud the diligence and hard work from my colleagues listed here. I'll go through them.

Dr. Angel Paredes, for collating the cryo-EM standard practice for characterization of liposomes; Dr. Tariq Fahmi, for multiple in vitro test methods; Drs. Ammu Matthew and Nathan Koonce for their contribution towards developing a guide on hyperspectral imaging; Drs. Goutam Palui, Achyut Raghavendra, and Sanghamitra Majumdar for collating the liposomal lipid quantitation standards. I would also like to acknowledge colleagues from NIST, NCI, NIEHS and USP, and international entities for helping with their development.

One of the most challenging aspects of nanomaterial assessment is surfaces. We have many methods for measuring size and drug loading, but then the complexity of surfaces and heterogeneity and with targeting ligands, is something, a question that has not been addressed. This is a significant knowledge gap for

emerging complex targeted nanomaterial that we see coming through FDA.

There are limited analytical methods and methodologies for evaluating these targeted nanomaterial from a product quality and reproducibility and binding ability standpoint. So this is a question often raised from regulatory agencies and submissions, so we have taken up a model with a pre-synthesized RGD peptide polyethylene glycol conjugated to a gold nanorod, to evaluate radiation enhancement and DNA damage in vitro. As a standard practice in the lab, we evaluated incoming commercial polyethylene glycol starting material, these are bifunctional, and during this process we learn that the commercial bifunctional PEG derivatives are not what they are supposed to be and do not have these functionalities. This is a problem, especially when you take something for granted and then conjugate these targeting ligands and then attach them to the nanoparticle. So we undertook revising this whole project and synthesized the targeted PEG derivatives ourselves to evaluate the targeted ligand binding, to immobilize the integrin using quartz crystal microbalance. Again, these are new methods, these methodologies are not extensively available, but are much needed.

Hopefully these methods we are developing are going to be robust and to test the replicability for other targeted nanomaterial, and once we can standardize them, they will be used further for in vitro studies and also to evaluate products and training.

The last time we presented to the Scientific Advisory Board, I guess in 2018, my colleague Dr. Angel Paredes highlighted the advantages and challenges of 3D imaging of biological specimen using advanced serial block face scanning electron microscopy available in our labs. We acquired this instrumentation over 10 years ago, and the bottleneck is the analysis of the data and reconstruction, 3D reconstruction of these data. So we recently acquired a new software that utilizes machine learning algorithms to analyze the 2D data, to elucidate the 3D ultra-structures of interest, to understand biological mechanisms. We have this facility available for FDA researchers, collaborating with other divisions at NCTR, and also support other centers at FDA. We hope that this software is going to address the bottleneck and we look forward for additional collaborations with the centers.

The next three slides I would like to highlight the scope of our future work and appreciate suggestions, guidance, and feedback from the SAB. As I mentioned on standards development, we are currently planning interlab

studies for precision and bias with existing test methods. Once the test methods are published then this is a requirement from the ASTM international and we are working on the liposomal lipid interlab studies using HPLC, CAD, ELST, and mass spectrometry detectors. We proposed a few new work items for standard development on surface measurement, as I mentioned. That's one of the priorities. The drug component and drug release test methods that are slated for development, as are the measurement of encapsulated and free components.

We plan to continue in vitro test methods, as well. They hopefully will bridge the gap between in vitro, in vivo correlation, and there are many challenges with in vitro methods standardization, but I won't go into those details. But we work through the subject matter experts to develop these methods.

Another current and future project that is being considered by the National Toxicology Program for funding in significant collaboration within FDA with CFSAN, CVM, ORA, and other government agencies, is micro- and nanoplastics. Maybe many of you came across the topic recently. There is a global interest in the micro/nanoplastics. These can be engineered or result from degradation of bulk plastic waste, with their indicated presence in FDA regulated products. Or at least they have

been published and then shown to contain these micro/nanoplastics. But methods and methodologies for their characterization and quantitation, especially in complex matrices, are nonexistent. Given the greater variety of the compositions of different kinds of plastics, different degradation from small nano size to micron size, in matrices, complex matrices, is a significant work and we don't have standards yet.

Unless we have those thorough quantitation, we cannot really do risk assessment. So we are embarking on this project after conducting a thorough scientific review by CFSAN, organizing many workshops to understand the status of science with clear identified need from multiple stakeholders. Again, this will be considered for hopefully funding from NIEHS NTP.

We understand that we have developed many of these methods over the years, but some of these we would like to continue that include immunotoxicity of nanomaterial, and develop greater understanding of the multifunctional complex nanomaterial that means that they include targeted drug delivery systems and methods therein, depending on the need from CBER and CDER, we plan to get into further understanding of gene delivery systems, with the recent success of, for example, lipid nanoparticle and RNA vaccines.

Some of the challenges is keeping up with the pace of nanotechnology development. Recruitment, all the divisions are bringing up, SAB is already aware of that, and the high cost of equipment maintenance for NanoCore. These are some of the challenges I would like to bring up.

We appreciate the feedback and the expertise with the Scientific Advisory Board and would like to get your feedback on what areas we should focus on with limited resources, any blind spots that we are missing, and we look forward for any suggestions and any collaborations that you think would be most useful.

That's it. Thank you.

DR. GANEY: Thank you, Anil. Looks like Greg has his hand up.

DR. LANZA: Great talk, Anil. One of the things I wanted to suggest is that there is a tsunami of nano stuff coming through our journals, particularly the WIRES journal I edit. And one of the problems I think remains is that the quality control of what they're making is lacking. And this is lacking not only for the components that may not even be in the particle like they're saying, or the presentation of the component, but I think that even the retention of drugs in circulation, so on and so forth. And I wonder if there's a way that the methodologies you're working with, and especially since they're international,

can become more available through local CROs or whatever, that people who make these technologies can send out and afford to have them tested for purity and potency and are all the parts in the particles, and so forth, at places near to them regionally.

DR. PATRI: That is a good question. Thank you, Greg. So, from a CRO standpoint, or making these available -- we have several avenues that we publicize this research either through presentations at conferences, but most importantly, as I mentioned, the standards, once we develop the standards, CROs will have access to these standards and then they can utilize these standards. USP, the United States Pharmacopeia, is getting into some of these liposome-related standards because they became generic products, and the recent CBER/CDER guidance was published last year about FDA's role or FDA's guidance on drug products that contain nanomaterials. So some of these are all available, and hopefully -- we are slowly getting these complex products, most of them are single entity material, for example liposomal drug products, but then as these methods become more complex and the submissions become more complex, this is something that we have to engage with others to make sure that they are, that the quality is maintained.

DR. LANZA: So, the situation is these concepts I'm sharing with you are things that are going towards clinical trial where people are taking platelets and membranes or other type of cellular membranes, encoding those, they're complex, they're using extracellular vesicles. They're supposedly for drug delivery -- they have no clue what's actually in there, and what it's doing or how it's working, and they're not well characterized, how much protein, how much lipid, and so forth, and the list goes on and on.

As a result of it, the field can be misled, like you mentioned about the liposomes for Doxil, and I just wondered if it's not -- if it's not your responsibility or the government's responsibility to help lead the way on better quality control, because I think a lot of times they're taking two steps forward and one back, or maybe two back, because of this lack of understanding what they're making and how to test it. And it's not just simple classic particles.

DR. PATRI: I can bring up two more points to that. Last year, there is a nano day, October 9, 10 to the negative 9, and it's considered as a nano day in the United States. We organized a workshop to specifically address these kinds of questions from small businesses. This is from Center for Drugs and through the Small Business

Industry Assistance Program. We had a whole-day workshop that's available publicly, and anyone can access that and look at what is needed. So that is, again, mainly to help small businesses. Of course large industry or pharmaceutical companies also get benefit from that.

The other thing is we always ask -- I can't speak for CDER, but I can speak generally from the Nanotechnology Taskforce standpoint, that we ask those that are interested in bringing those into clinical or IND applications, to come to FDA with a pre-IND application early on, so they may have developed some material, conducted some in vivo studies, and they have a concept, and at that stage they can come to FDA with the pre-IND submission and get a good review. And that's when the FDA reviewers can ask appropriate questions that can guide these product developers to come to FDA.

DR. LANZA: I see. Thank you.

DR. GANEY: Anil, I have what I think will be a quick question. I noticed when you were discussing the plastics that you had as a goal detection, identification, and characterization, but I didn't see anything about toxicity assessment. Is that something you might partner with one of the other divisions to think about doing sometime in the future? Or not?

DR. PATRI: Maybe not. This is really a complex project, so we are working very closely with the Center for Food Safety and Applied Nutrition, and at least in the foreseeable future, we first need to know what is in the products. In other works, if fish take up these micro/nanoplastics thinking that they are food, what needs to be tested in vivo? First of all, we need to know what is there, what needs to be tested, before any toxicology can be done.

The literature right now is mostly on polystyrene particles because they're commercially available, whether they're micron sized or nano sized. But what we would rather have is to have the understanding initially, so we decided -- again, this is in internal dialogue within FDA -- not to conduct toxicology studies but initially focus on the material measurement methods to identify and quantify these micro/nanoplastics present.

And then if academics are going to run those toxicology studies, making those appropriate degraded micro/nanoplastics available to them. And again, NIST is developing standards in that area. So we consciously made a decision not to get into conducting toxicology studies at this point.

DR. GANEY: Thank you. If there are no other questions, I think we are just going to move ahead with our agenda, and we will now hear from CFSAN. Thank you.

Agenda Item: Center for Food Safety and Applied Nutrition

DR. FITZPATRICK: Thank you for inviting me here to talk about what's going on with our partnerships with NCTR to advance regulatory science.

The regulatory mandate of the center is very large. We oversee about 90 percent of the food supply -- that's direct food and color additives -- and food contact material -- direct food and color additives and food contact where we do have some regulatory oversight, but we also see other cosmetics, dietary supplements, GRAS compounds, botanicals, contaminants, and constituents in food such as metals. Constituents are all of those heat processed contaminants that end up in food -- furans, nitrosamines, acrylamide. In fact, anything that's in water or soil ends up in your food somewhere.

So people are exposed to food and contaminants in food, chemicals in food, every single day. Maybe several times or many times a day, but FDA has not been given a lot of preapproval regulatory tools to look at them, so we're very -- our partnership with NCTR has really helped us

develop these new tools so that we can decide what's safe in food.

We partner with NCTR in several critical research activities that advance our mission. Closer to Zero, which is trying to lower the level of contaminants in babies' food, like the metals, which are all developmental neurotoxicants. And CBD, cosmetics, and models for dermal absorption. And Tucker mentioned this briefly, a rapid risk framework for identifying contaminants in food.

Oftentimes and recently, there have been food sources that have caused toxicity, and we either can't identify what the toxic element is, or we can't develop what the toxicity is, and we need a rapid risk framework in order to do this. We can't go back to animal studies and wait two or three years to determine whether something that we've identified or someone else has identified, in food, could cause a problem to consumers.

One of the things I mentioned to you is our Closer to Zero program. We picked up lots of different baby foods, foods that were either labeled or commonly eaten in babies and children, to look at the levels of arsenic, cadmium, and lead in those. All of them are located in those baby foods, as a mixture, and we all know that they also can cause developmental neuro effects to

babies and children, potentially, depending on the level in food.

One of the things we did a couple of years ago, Dr. Talpos' group did a very nice behavioral study in rats, but that took several years, and we need quicker methods in order to look at these -- either alone, like the study we did in zebrafish, or together as a mixture, because they're found as mixtures in food.

So this is a study that Dr. Talpos did, Jyotshna did, for us, to look at the effect of inorganic arsenic on several different life stages of zebrafish. She did find some effects on zebrafish from exposure at levels that are not that much higher than you see in food right now, and you can see we published this paper, inorganic arsenic alters development of dopaminergic neurons but not serotonergic neurons in motor neurons development. And so we're continuing this work and what we want to do is look now, can zebrafish be a tool to look at mixtures of metals at different levels, to see what effects they have.

What we do actually with NCTR is we come to them with a research question, like we did with the zebrafish, and can you help us use it as a tool for Closer to Zero? Another area that we look at is tattoo studies. Now, tattoos are considered cosmetics, and they're used by a lot of people, but they're not made for humans, they're really

made for cars and other commercial products. NCTR did some very nice studies on this to look at microbial contamination of the tattoos that are commonly used by people, and develop some regulatory methods to potentially develop these harmful tattoo -- and remember, these tattoo pigments, once they're applied to the skin, very quickly become systemic.

They were looking at the distribution and placental transfer of tattoo pigments in mice. That's one of the things we're trying to look at, so we know that the tattoo pigments may go into the lymph nodes of adults when they're added, but are they really crossing the placenta and affecting the fetus? And that's a project that they're working on, first with mice and I think with other -- they're trying to do it with some other animals, and I think Fred is going to be reporting on that later today.

That's very important, if not only are we making a choice for ourselves in getting tattoos, but also making a potential choice for our children. So we're pretty excited to see how that comes out.

One of the questions that you asked, in our mind at CFSAN, we should start with a regulatory question, and then work with our labs or with NCTR to help us find an answer of that question, and for cosmetics, the first question that you ask is, is it dermally absorbed? How

much is it dermally absorbed? And if a lot of it becomes systemic, you're going to have to do the same type of systemic testing as you would for any oral product that you consume.

So Luisa is looking at whether comparing the performance of 3D bioprinted skin and other alternative skin barriers with excised human skin that is usually used, tummy-tuck skin. She's workings with NCATS on this to decide whether these are better models than the tummy-tuck skin, which is becoming pretty hard to acquire. And if so, which ones could be used? So this has been really great work that she's doing in conjunction with NCATS, where we've got some Office of Women's Health funding and we're looking forward to hearing the answer. Maybe not anymore at CFSAN, because cosmetics is going up to the Office of the Chief Scientist. But nevertheless, it's really exciting and this will answer questions as to whether we have to do systemic testing or we can use a TTC approach if the cosmetics are not that dermally absorbed.

Also she's looking to look at the dermal absorption of CBD and its major metabolites in Sprague-Dawley rats. CBD and its metabolites are located in cosmetics, it's one thing that we've asked them to look at. It's in creams, oils. We know it's absorbed through the skin. We want to see how it's distributed and what type of

exposure there is. So she's helping us, the FDA Office of Cosmetics, evaluate the bioavailability and the metabolic profile of CBD.

Additionally, we had heard that CBD might be a developmental neurotoxicant, especially to males, and we've asked NCTR to look at the exposure in rats of CBD gavaged daily, and to look at both the developmental effect, looking at the brain, see where it goes, doing some neurobehavioral testing, and evaluate the neuroimmune effects of CBD. And that study's going on right now.

In addition, we want to look at the -- see if we can develop an in vitro evaluation of male reproductive toxicities induced by cannabinoids and its main metabolites. If there's a lot of interest in putting CBD in food coming in through the GRAS program, which is not a notification program which people can put on the market without actually CFSAN. However, if we feel that any components of a GRAS product, including CBD, has some toxicities, they're not eligible for the GRAS program. So we're very interested in looking at both the animal and the in vitro evaluation of male toxicities with the cannabinoids, and looking forward to hearing about that research.

Another project that we're interested in is looking at fetal and neonatal toxicokinetics of the 6:2-

fluorotelomer alcohol. We want to develop a strategy to look at methods and criteria for characterizing compounds that might become biopersistent and therefore -- which is not something that we were looking at originally, so this is another area where we got a challenge grant and we're working with, we worked with NCTR, and we have a manuscript in its final stages of preparation. And if you have any questions in detail about these, since I wasn't the one in the lab, you'll have to ask NCTR. But I think that will all be presented.

Those are just some of the examples where we've gone to NCTR to do research that we can't do ourselves in our labs, and which will answer really critical questions about the food supply. And I can tell you that NCTR steps up every time to really help CFSAN in this area. In fact, last night, as they're getting ready for this Science Advisory Board, Tucker, Goncalo, John Talpos, and others, were willing to meet with CFSAN about another contaminant that we think may be coming from water into food, and which could potentially a very large problem for everyone. So I think that the gratitude that we have to NCTR for always being there for all of these questions that we have, regulatorily, for the food supply, we're really grateful to them.

In addition, there is a CERSI that comes out of the Office of the Chief Scientist that looks at leveraging human brain organoids for looking at mixture toxicity, including mixtures of metals. It's called the BrainMixTox toxicity -- it's a CERSI that the money was given to Hopkins, and with that we're evaluating the different results that they're doing. So CFSAN, other parts of the Food and Drug Administration, NCTR, are all looking at this project in the process, not only having neuro sites, they have glial cells and microglia, and they're using this as a way of using artificial intelligence, and more importantly, teaching these organoids to think, and organoid intelligence, which is exciting and scary at the same time, and I think, this is a project that CFSAN brought up because we're looking at mixtures of metals, and could apply into Closer to Zero. But also we've asked for NCTR's help in evaluating this project.

The goal of the BrainMix is to look at the impact of metal mixtures and gene-environment interactions and susceptibilities and the developmental neurotoxicity of these brain organoids, and to understand mixtures of metals, and sort of use maybe this as a DNT tool to look at a novel risk assessment of mixtures of metals, which is a very important issue for us because of the presence of mixtures of metals in food, including baby food.

NCTR is also the FDA interface at the National Toxicology Program, and this is no simple task that -- and falls mainly on the shoulders of Goncalo to really include our interests in this partnership with NIEHS and NIOSH, in addition to all the other centers. We really appreciate him because he helps us work with NIEHS to develop some of these tools that we need to look at these contaminants in food. And also to make sure that any reports that NIEHS or NTP generates that includes CFSAN products or things that we're interested in, we have the time to adequately review them and comment on them before they become public. For that we're very grateful for Goncalo, in addition to the research he does for us, to do this really important job. And not always very fun job.

The other partner that does a lot for us is Donna Mendrick. She does more than run the SAB. She actually with me chairs the FDA's Alternative Methods Working Group, which was the first time that FDA as a whole agency got together to talk about how we're going to move forward with alternative methods. Not only did we develop -- we worked on as the toxicology working group, all together, the predictive FDA toxicology roadmap, which to me was very surprising that it's been quoted internationally, and if I'd known that I would have put a better cover on it than that test tube.

Then we developed another report in 2021 to show FDA's commitments and discussions of all the in vitro data that we have going on now. We also developed an Alternative Methods Working Group public website, and most of the credit really goes to Donna for really keeping, for the first time, a public website where our stakeholders can see what we're doing in alternatives, and the alternative methods workgroup also created a place for people developing alternative methods that are pretty advanced, that have a context of use, to come and present those to FDA. And again, most of the credit, or even all of the credit, has to go to Donna Mendrick, because she's really run this project for two or three years and has brought a lot of new and exciting methods to the attention of FDA, for which some of them, including some from CFSAN, have been adopted by us to help develop as more of a regulatory tool. So this is another big job, including all the things she has to do at NCTR, that she does for the FDA.

We also have what's called the global harmonization of food safety, which is ILMERAC, which is a working group that we put together with CFSAN, EFSA, other countries, Canada, Japan, Korea, China, and we formed a working group on new approach methods, which NCTR is a very active member of this group, and we're looking at really the same things we're looking at in NCTR but on a broader

scope and for food safety to harmonize it across the global sphere, and we're looking at mixtures, because as I said everything in foods is a mixture. Relevance of new approach methods for risk assessment, and developmental neuro, and also organs on a chip. Again, NCTR joins FDA and CFSAN in looking at this global harmonization group.

I don't know how many of you are familiar with what's going in Europe. They had EU-ToxRisk, and once that was closed they were funded for a big program called ASPIS, which is accelerating the pace of chemical food safety, and one of the programs is called Risk Hunter. There's three programs, Risk Hunt3r, ONTOX, and Precision Tox. CFSAN represents FDA on the international regulatory committee, so at that last SOT meeting we met CFSAN and NCTR met with RiskTox to look at some joint projects between FDA, NCTR/CFSAN, and the Europeans, a joint project on microphysiological systems, on quantitative AOPs -- I think adding quantitation to AOPs may make it a good regulatory tool to look at mechanistic relevance. And then threshold of toxicological concern.

And I might add that Donna Mendrick, she oversees a CRADA that we have with Emulate on several different microphysiological systems under Emulate in several of our centers, including CVM, CDER, CBER, and NCTR, along with

other chips that we have at NCTR, including the tissue chip from Germany.

What we've asked NCTR to help us with is the commitment that we made to Risk Hunt3r to look globally at the same compounds in these different systems, in the different microphysiological systems that we're going to see here at FDA and in their systems in Europe, to compare the results.

It's always nice to see Dan Doerge, we miss him a lot, but I included this slide because I wanted to demonstrate that Dan was just awarded this 2023 Philippe Shubik Award for Distinguished Scientists, for all of the toxicology work that he did, and most of it was for CFSAN, and I think it's really great to see research that we asked him to do that really helped our regulatory programs also being recognized in a prestigious society for his work. So I was just lucky enough to be there to be there to help present the award to him, and once again we're really grateful to Dan to all the work that he did and all the work that NCTR has done for us.

We'll just end by, and I'm sorry I'm really great at getting into the details of all the research, but CFSAN works collaboratively with NCTR and with our stakeholders to answer these regulatory questions, and our role, and I have millions of questions, is to identify our regulatory

questions and then help work with the scientists at NCTR to help us answer them.

By identifying these critical priorities and working in partnerships we're better able to meet our mission and assure greater quality in the food supply that touches everyone, every consumer in this country and globally. So with that, thank you very much, and thank you for inviting me here today, and most of all thank NCTR for its great work for CFSAN.

Questions? I guess I put you all to sleep maybe.

DR. GANEY: Ken, you look like you might have a question or comment.

DR. RAMOS: I do have a question, thank you so much. I actually enjoyed your presentation very much. You did not put us to sleep. I was intrigued by a comment that you made and I hope that you can elaborate some. When you were talking about the organ on a chip, the organoids, for the brain, you said that they're making them, for them to think.

DR. FITZPATRICK: Yes. You should have seen John Talpos' face as we heard them go on and on about organoid intelligence, and they just -- this is at Hopkins, and they actually have a journal now and a paper in Frontiers in Toxicology out about that, where they're trying to somehow make the organoids, teach them to think. Which is exciting

and scary at the same time, and they have an ethicist that's working on them to see how far they can go on that.

DR. RAMOS: And that was published, you said, in Frontiers?

DR. FITZPATRICK: Yes, Frontiers of Toxicology, I think it just came out, from Hopkins. Actually, we were kidding that eventually the organoids' avatar will just present data and all of us scientists will become superfluous, because it will present its own data. But, yes, that's one of the things they're working -- that's not what we asked them to do. We asked them to look at the effect of mixtures of metals on the brain, using these little mini-brain organoids.

DR. GANEY: Suzy, thanks for your presentation.

We will now move onto the Center for Tobacco Products.

Agenda Item: Center for Tobacco Products

DR. VAN BEMMEL: Great, thank you so much. Thank you for the opportunity to be here today. I'm Dana van Bemmel. I'm the chief of the Research Operations and Advisory Resources Branch at FDA's Center for Tobacco Products.

I'm excited to be with you today to talk a little bit about the center. I'm going to talk with you at a high level about what we do, talk about our research program as

a whole, and then talk about how that intersects and the collaborations that we've had and hope to continue with NCTR.

I'm going to start just by reminding folks, I think many of you have heard parts of this before, but at the Center for Tobacco Products, our overall goal is to reduce the harm from tobacco products across the entire U.S. population. And when we think about that, the safe and effective standard that FDA uses to regulate other products under its authority, such as drugs and medical devices that we've heard about today, does not apply to the regulation of tobacco products.

Under Congress's direction, FDA uses a public health standard that considers the risks and benefits to tobacco products on the U.S. population on the whole, accounting for the potential impact on both users of tobacco products and nonusers of tobacco products. So, slightly different, but overall similar to other regulatory centers.

We're a relatively new center compared to the other centers here at the FDA. CTP was established in 2009, the signing of the Tobacco Control Act, and at that time we regulated the manufacturing, marketing, and distribution of cigarettes, cigarette tobacco, roll-your-own, and smokeless tobacco products.

In 2016, the FDA finalized a rule that is commonly known as the deeming rule, that brought all products meeting the statutory definition of a tobacco product under our regulatory authorities. And I think the most notable product to folks here that was not regulated until August of 2016 were the e-cigarettes, the electronic nicotine delivery system products, or ENDS. But it also included bringing all cigars, pipe tobacco, and water pipes under our regulatory authorities.

One more note for what is currently under our regulatory authority is in March of 2022, the President signed a bill to include language amending the Tobacco Control Act, to bring nontobacco nicotine, more commonly known as synthetic nicotine, under FDA's regulatory authorities. Up until that point, the Tobacco Control Act had defined a tobacco product as those containing nicotine derived from tobacco specifically, so this allowed for products to be marketed without FDA review that contain synthetic nicotine. So that was prior to March 2022. Now these products are under our regulatory authorities and under our review.

Before I get too far into the center and our research program as a whole, I wanted to just take a moment because it's been a big year of change within the Center for Tobacco Products. This year we have a new center

director and a new office director within the Office of Science. Brian King joined us in July of last year, I believe, as our new center director, and it's been exciting to see the direction. I'll touch on some of his strategic priorities that have been rolled out over this last year as we move through this slide presentation. And just this last month, actually, just a couple of weeks ago, Dr. Matthew Farrelly joined us as the new director for the Office of Science.

Both of these individuals are coming to us with decades of tobacco experience in tobacco research and tobacco control, so it's great to have them on board and will be exciting to see how their direction takes and shapes the Center for Tobacco Products, and specifically our research program, which is where I think and work most days.

Like many of the centers that you've heard from already today, it's science and research that informs all of our regulatory activities, and here on this slide at a very high level, I'm just trying to give you a snapshot of the regulatory activities that the Center for Tobacco Products in active in, including rulemaking, which includes guidances, which some of the centers have talked about, and product standards development. But also includes compliance and enforcement activities, application review -

- tobacco product application review activities -- and communication and education activities. And again, at the foundation of all of these activities, the decision-making, the review, it's the tobacco regulatory science and the data that is driving our decisions and our actions.

I have had the privilege of working with the Center for Tobacco Products research program since 2011, and in the time since its very first project was funded in fiscal year 2010, the Center for Tobacco Products has funded over 600 research projects. The majority of those projects, more than 60 percent, sit within a collaboration that I'll touch on in a few slides, but they are NIH grants that we fund through a partnership with the NIH Tobacco Regulatory Science Program. But that leaves 40 percent with all our other collaborators, including our federal partners, including NCTR.

We have had, since the very beginning, a thorough evaluation program in place, to be monitoring and tracking the impactfulness of the tobacco regulatory science that CTP funds, and we know that through fiscal year 2022, we have funded projects that have resulted in more than 3,600 publications, 400 of which were funded just last fiscal year, and I'll touch on a few that are NCTR-related later in the presentation. But really it's been a fantastic program to be a part of, to be able to stand up a research

program such as this, and to see it grow into such a impactful program has been really exciting.

Unlike some of the other centers that you've heard from today, the Center for Tobacco Products does not have its own research lab. So we fund our research and perform the majority of our research through collaborations, and those include collaborations with other federal agencies and partners. It includes federal contracts, and it includes activities with other non-HHS organizations, all of which have particular expertise and are able to answer specific tobacco regulatory science priority research questions that we have. This slide isn't all-inclusive, it's just to give you a sense of the types of partnerships that we have within the research program.

I know we're here to talk about NCTR, but it felt like we needed to just touch briefly on this large piece of our research program as we talked about, which is the partnership with NIH. We partnership with the Tobacco Regulatory Science Program, which sits within the Office of the Director, and they are able to work with across all institutes at the NIH to help fund research projects that are specific and answering tobacco regulatory science research questions. This includes a large research program known as the Tobacco Centers of Regulatory Science, or TCORS, which are large cooperative agreements made up of

three to five research projects independently. They are funded, they are five-year projects funded at several million dollars each year. It's been a really successful program, and again a large part of the research that we do, but of course, not all.

I mentioned that we've been evaluating our research program for many years now. Just to give you a little insight into the impactfulness of the tobacco regulatory science that CTP is funding. We have two recent proposed standards that were published over this past year, one for a product standard for characterizing flavors in cigars, and a second proposed standard for menthol in cigarettes.

Of the overall peer-reviewed publications that were cited, we were able to identify more than 25 percent, or over a quarter of those citations, referenced CTP-funded publications, and you can see the breakout there. But again, we know that we are funding research that we are then using in our decision-making.

We also have scientific assessments. Scientists within the FDA Center for Tobacco Products have three main goals when developing the assessments of evidence related to the role of menthol in cigarettes, and that of characterizing flavors in cigars, the first of which was to provide a comprehensive and accurate review of the

available science. The second was to provide documentation of the scientific approach to allow for reproducibility, and the third was to ensure transparency in the scientific approach taken in the development of these proposed rules. I share this just to give you a sense of the types of research that we are using in our regulatory activities, and copies of these three assessments along with peer-reviewed reports, detailing the peer reviewer comments and FDA responses, can be accessed on the FDA.gov webpage.

I mentioned we have a new center director and Brian King has been great at really focusing us, not that we were unfocused before, but really focusing us on four key priority areas that he has identified as our new center director, and that includes stakeholder relations, communications, work in health equity, which includes research in this area, because we know that disparities in use, particularly of combusted tobacco products, can lead to disproportionate suffering from tobacco-related death and disease among certain populations.

And despite the tremendous progress in smoking prevention and cessation over the past 50-plus years of tobacco control activities, the benefits from those efforts haven't been experienced by everyone equally. So he really has put a focus on health equity and health disparities as it relates to tobacco use for our center and our research

program. And then of course his fourth priority area is sound science. Again, acknowledging that that informs all of our regulatory activities.

The Center for Tobacco Products currently has eight research priority areas identified on our website, and if you're interested in the details that falls under each one of these, the link is here on the slide. But just to note that we have identified a breadth of research priority areas, and they cover and represent the type of scientists that we have here within the Center for Tobacco Products, like some of the other centers that you heard from earlier today. We have population scientists and social scientists, and clinicians, and laboratory scientists, lawyers, and all the gamut, all coming together to regulate tobacco products. So we certainly acknowledge and have research priority areas in a number of areas here focused on this slide.

I'd like to take the next 10 minutes or so of this presentation to talk with you a little bit about some of our collaborations with NCTR. As I noted on the previous slide, we have eight research priority areas. There are three key priority areas that tend to focus our research activities and collaborations with NCTR, and should be no surprise that the top one there included is toxicity, toxicological assays, to compare toxicity across

different types of tobacco products. But we've also worked with experts at NCTR in addiction work and looking at the health effects of tobacco product characteristics, including product design, e-liquid design, on health.

Then other area that we have a number of research projects past and ongoing relates to informatics, and we heard already today about that informatics program, so I don't want to dwell too much on it, other than to just note that this is a key area that we have been partnering with, that allows for the expansion of search tools and CTP to do their regulatory activity.

When I think about our program and our collaboration with NCTR, it really falls into three areas. We have inhalation work, whole smoke and ALI work or air-liquid interface work, and then informatics. So I'm just going to take a few moments to step through those three buckets, if you will, and highlight some of the projects that we have funded.

When I think about the InhaleCore, some of the more recent work that has just been completed includes work in aerosol inhalation developments, pharmacokinetic analysis around nicotine exposure, and then a five-day nicotine inhalation tox pilot study. Collectively, these three completed inhalation projects developed a tiered aerosol inhalation model, established the distribution of

nicotine following exposure in three models of exposure, including intravenous, oral, and inhalation. And then we confirmed the tolerability and feasibility through the pilot work of a three-hour nicotine exposure paradigm. All of these projects will inform an exposure modeling work and additional inhalation tox projects that we are hoping to move forward.

The second area that we work closely with NCTR on is around the ALI work, as I mentioned. Our most recent project that was completed around this work was the validation of the in vitro exposure system. The validation procedures established here in the performance characteristics looking at repeatability and reproducibility and testing the limitations of the in vitro cell cigarette smoke and ENDS or e-cigarette aerosol exposure systems will enable CTP and NCTR to conduct additional exposure experiments related to ALI that mimic in vivo exposure conditions, allowing us to assess further toxicological impact of smoke, aerosol, and in vitro.

You'll notice that I have a slide here that says completed, but I'm talking about work that is planned. We are in between actively funded research projects, but we certainly have research projects that are funded in fiscal year 2023, we're just logistically in a sort of in-between

space. But these are certainly informing these future projects.

And finally, we work closely with NCTR on different informatics projects. The most recent and current projects that we've been working on is to develop a search tool for tobacco product marketing applications that will provide accurate answers to user queries. The system uses artificial intelligence or AI-based natural language processing models to provide deeper search capabilities using the language model developed to represent relationships between words and concepts within a body of a text. Clearly, the staff gave me this information to help me understand exactly what these projects are doing, but at a basic level, as I understand it from our scientists and our informatics group. This is helping us really search through thousands and thousands of pages of documents to identify information within tobacco product applications. So it's been a very important and a very successful collaboration.

Just to note that the success of some of these projects, I wanted to highlight just some of our recent publications. We heard earlier from Tucker that the average number of publications coming out of NCTR, and it's nice to see from our collaboration that some of those

numbers that he shared represent collaborations between CTP and NCTR scientists.

I mentioned we've had a number of successful collaborations and we have a number of projects in the works. We have projects within each of those three core areas that I mentioned, including inhalation toxicity studies. Our hope is to look at some toxicity with repeated exposures to hazardous and potentially hazardous constituents. We'd also like to use these models, both the ALI and inhalation models, to look at flavors in tobacco products, to be able to look specifically at the chemicals or the constituents in the tobacco products themselves or in the e-liquids, and also what chemicals and what compounds are formed upon heating and combustion, depending on the tobacco products being looked at.

We also hope to work with NCTR, again, in the ALI space to be able to look at cytotoxicity and genotoxicity around aerosols generated from specific electronic nicotine delivery systems, again, using this ALI system. And to be able to simulate human inhalation exposures with that ALI culture, again, to look at specific tobacco products. I believe our focus over the coming year will be on e-cigarette products. But we do hope to expand at some point within our research portfolio to be able to be looking at additional research projects. We have some in the

portfolio already, but additional research projects around nontobacco-derived nicotine products as well.

Before my time is up, I did just want to take a moment to note another key activity that happened over the last year, and that was the outside, the external evaluation of the Center for Tobacco Products. In July of last year, the Commissioner announced plans for CTP's evaluation by the Reagan-Udall Foundation. Their report came to us in December of this past year, and in February of 2023, FDA released plans to address recommendations. There was a statement both from the Commissioner's office and from the Center for Tobacco Products.

I'm not going to dive deep into what each of these areas covers. If you're interested in that it is publicly available on our website, but I did want to note that within those key areas of focus that our center director has acknowledged we will be focusing on as a result of this Reagan-Udall Foundation evaluation and report, it includes science and application review. So again, science and research is where I spend my days thinking, and I wanted to note it here just as we continue to think about the research that we are funding as a center and our collaborations with our federal partners including NCTR, there may be additional information in the coming year related to these activities.

Before I go, I just want to thank our collaborators at NCTR, specifically the liaisons that make these projects possible, and all of the leads that were noted on the slides and I'm sure that we will hear about and have heard about the projects specifically. I'd just like to echo Suzy's comments that we really appreciate the work that NCTR does with us, and as I noted, we don't have laboratories of our own, and so we need strong scientific partnerships, and we really appreciate our collaborations and the research that we are able to do with our partners at NCTR.

There may be one last slide. Yes, the standard questions and contact information for CTP. With that I can take questions if there are any before the break.

DR. GANEY: Thank you, Dana. Very nice presentation. Are there any questions for Dana?

I think we are going to march along and hear from the Center for Veterinary Medicine now, and we'll take a break after we hear from the Center for Veterinary Medicine, Regina Tan.

Agenda Item: Center for Veterinary Medicine

DR. TAN: Good afternoon. Thank you for inviting me today. I came to talk with you last year around this time as the director for the Office of Research for the Center for Veterinary Medicine. I'm now coming to talk

with you from the Office of Applied Science, and I'll talk with you about those developments soon.

I'll give you a quick update. I'm also going to talk with you about current collaborations. But what I'm really excited to talk with you about is future steps.

What is remaining the same is the Center for Veterinary Medicine's mission in protecting human and animal health. This is my job, which is strategic alignment of our research with our regulatory functions, and that is safe and effective animal drugs for companion and food-producing animals preapproval, monitoring safety and effectiveness of animal drugs on the market, making sure animal food is safe, made under sanitary conditions and properly labeled, making sure food additives used in animal food are safe and effective preapproval, and helping make more animal drugs legally available for minor species. Minor species are things like rabbits and fish. As well as the infrequent and limited uses in major species.

This is our reorganization. What this really does is I've aligned all of our functions in the same divisions. So all of our chemists are now within the Division of Residue Chemistry, which allows us also to take all of our instrumentation, our chemistry instrumentation, put them in the same division, and employees are supervised by a chemist, as well as making sure that we can gain some

cost efficiencies. A lot of cost efficiencies that we're looking at this way. And this is really what's bene done around the entire office.

It's not very exciting to talk about functional alignment, but what's exciting for me is the costs that we are able to recoup so that we can actually then put those costs directly into research, and I'll be honest with you, paying for maintenance contract on my mass specs, that money is necessary money, but what's more exciting expenditure of that money is actually paying for more research instead with that same amount of money. And this realignment is allowing us to do just that.

What you don't see here is you don't see a division of toxicology. One of the themes that you're going to see throughout our discussion today is that I'm really honestly looking for partnership with our sister organizations. Rather than building a capability myself, I would prefer to partner with another organization that already has that capability. So I'm not going to be having a division of toxicology; we'll just call NCTR.

The strategic goals for the Office of Applied Science are really supporting the availability of safe and effective animal drugs, advancing food safety and safe animal food products, supporting One Health monitoring investigation and response. We do have those epidemiologic

functions within the Office of Applied Science. And advancing emerging technologies and innovation. Those goals have not changed. What we've really been doing is working very hard on number five, improving business processes and operations to enable excellence in science and research, and then fostering the One CVM culture across organizational boundaries.

Last year I talked with you about the alternative methods community of stakeholders that is within the Center for Veterinary Medicine. We do align with and support the agency-level work that Suzy and Donna lead. And we are very happy to do that. We have made great strides in the last year, and we're at the point where we are able to report not only that we are developing innovative methodologies, but really it's our goal that those innovative methodologies are made -- we lower the bar, so that animal industry can then adopt those themselves.

For example, we're just collecting the numbers. We're using laparoscopic methodologies, rather than sacrificing animals for certain testing, and we can save 96 animals in that research. That's a little bit more than double what we would have used otherwise and about $250,000. So keeping track of the things, of the ways that new alternative methods can be useful, not just in reducing animals, but making it possible for industry to adopt these

things, attractive for industry to adopt these methodologies. That is what the alternative methods community of stakeholders at the Center for Veterinary Medicine is working towards. Because our target audience, they're animals, and we do still have to ensure safety and efficacy. We're not likely to ever eliminate it. But we can do our best to make it cost-effective and innovative for others to adopt it.

What's different between last year and this year is last year I talk with you about the One CVM culture across organizational boundaries, really meaning, like with the alternative methods, the Center for Veterinary Medicine organizational boundaries. But what I do want to talk with you about this year is expanding those organizational boundaries to include NCTR.

What's not going to change is our working style. We're always going to stop and align our portfolio of research within the center. We're always going to coordinate discussions at the center level, so that our developed science is aligned with our regulatory mission. We're always going to be looking to make sure that the offices are working collaboratively together to really make sure that we're all working in tandem for that CVM mission.

I'm going to give you a smattering of the collaborative projects that we have going with NCTR

currently. I know you're talking with the divisions, so I'm not going to go very deeply into them.

Our Office of New Animal Drug Evaluation has about seven projects right now with NCTR, and if you look over all of them, they generally fall into a couple of buckets. One of those buckets, of course, is going to be working for new animal drug evaluations. Those are very important to us. Those are our bread and butter, absolutely our bread and butter. They're wonderful, and we very much appreciate the collaborations that we do have with NCTR.

The other ones are really animal use, and when you look at our studies, there's also how do we use animals safely as models for human users. That also has come up in our collaborations.

Again, I'm not going to go into these deeply, I'm just going to let you take a gander at these. Next slide. And one more slide.

Next, I'll talk to you about one of our projects, collaborative projects, from the Office of Applied Science. This one, our NCTR PI is Ashraf Khan, and our collaborator within the Center for Veterinary Medicine is Shaohua. Shaohua, she's one of our SBRBPAS, so one of our very most senior scientists. She is extremely prolific in her research, and she tends to focus her research on the

evolution of mechanisms within bacteria that ensure their survival. This particular collaboration is working on the structure of multidrug efflux pump and their role in antimicrobial resistance in salmonella. And that makes so much sense, right? If you're a salmonella. Doesn't it make sense that when you have an antimicrobial in your system and you don't want it there, open the window and escort it out. So that's what they're working on.

These are the milestones that they've got to date. Essentially, they're taking a look, they found two genes that confer resistance to gentamicin. But those two genes are not always expressed, and they're not always expressed equally. Clearly, well, one would guess, and they can show, that when those two genes are expressed at the same time, there is an extremely high MIC for gentamicin, minimum inhibitory concentration, for gentamicin, which makes so much sense. There's more of the genes and so you have more resistance. The question now that they're working on is why are those two genes not always expressed at the same rate at the same time, and so they're going to be continuing to work on that.

This is actually where they get their samples. Their samples come from our National Antimicrobial Resistance Monitoring System. We actually take isolates from retail meat samples around the nation, and so we are

looking eventually to cover the entire nation. We're not quite there yet. We are really looking at things that people would find at the grocery store.

This is the part that I'm very excited to get to. A few months ago, I think it was last December, I asked Tucker if we could have a coordination agreement together. What I'm really looking to do is a formal understanding between NCTR and CVM. Again, if we had the capability, what I'm really looking for is to work with NCTR, so NCTR can have a compatible capability with ours and that our two organizations can be complementary. I'd like to outline the animal care and use responsibilities for each center, make sure we know who owns what animals, since we both have vivaria, and delineate the responsibilities of the respective IACUCs, the institutional animal care and use committees, so that we know how those two work together.

At CVM, we do have that model with other centers and with other organizations. Again, it helps to build redundancies. It also helps to build redundancies with animal care and with veterinary care and making sure that we can make the most of resources that we have. What we're also finding is it helps reduce expenditure outside the agency. So the money that we have available within the agency, we can get more out of. We're always looking to get more research dollars available, and if we can work

with another part of FDA rather than executing a contract to a contractor, we perhaps can get some cost savings there. And we are finding that to be true in other parts of the agency.

The opportunity so far that we see. I've talked with you before that we don't have a division for toxicology, so there is that part. Also, within the Center for Veterinary Medicine and NCTR, our vivaria have very different animal species that we have in-house. I will give you an example. We don't have rodents. We do certainly have rodent research, but there is space over at CBER, and so we currently have an MOU with CBER, and I pay rent, and my PIs go to CBER to do their research.

I would also say recently we've been asked if we can house shrimp or zebrafish in our aquaculture facility, and we don't have the facilities to do zebrafish at all, so I suggested they call NCTR. We also don't have the facilities to do shrimp. So there are always ways that laboratories can work together, understand who has what expertise, and just fit the pieces of the puzzle together so that we can partner.

One of the practical logistics for this, really what I'm looking for is our institutional officials to be on the same page. One of the things that we've been talking about is how do we make sure that we enable our

research scientists to express their creativity and work together to express creativity. That is a spark that we want to keep going. At the same time, how do we support that at an institutional level? And how do we make sure that both of our IACUCs are onboard together and aligned, not redoing work that the other one is already doing, but also everyone is in the loop. That kind of coordination is something that we can do, we have done successfully. We just have to lay the groundwork for it.

We also want to make sure there's clarification of terms across the organization. This means who owns the animals, which once you get into animal care, it's a very important part of doing research with animals, as well as responsibility for costs that are incurred by studies. If we can lay all of these things out together, that already sets the institutions to be on the same page, and it makes the way open for our collaborators to work together.

I think right now where this is, is we have a draft in place. I believe NCTR has taken a first cut at that draft and sent it to us. And our IACUC is going to take a look at it on Thursday, and then after that we'll be taking it back to NCTR for their review.

Points of contact. I'm the director as well as the institutional official. I knew Tucker was the institutional official in December, and my deputy director

is Chris Whitehouse. I also have to put my IACUC administrator up here, Andrea Kouneski, again, because what we're really looking for is to make sure that we can support research and we can support collaboration between the two organizations, together, and I can't do that without my IACUC.

With that, I think that is everything from me unless there are questions.

DR. GANEY: Thank you very much, Regina. Are there any questions about the Center for Vet Medicine? I'm not seeing any, so I'll thank you again. Oh, wait, Greg.

DR. LANZA: I just have one. That was a great presentation, and as a taxpayer I love you. But the thing that I wanted to ask is that NCTR doesn't have the ability for toxicology in ruminants, for instance. How do you make up that gap, because obviously it's a major part of the food supply, and there are changes going on in ruminants -- I know chickens are monogastric. What do you think about that?

DR. TAN: On campus, we do have the facilities, 198 acres of pastureland. Ruminant studies are possible with us. They do take a lot of time, and ruminants -- and I do understand -- ruminants, we mostly use cows, although we also have goats. Ruminants, are a species -- and food animals, they don't generally live out a nice long

lifespan. But the laparoscopic studies, those were in ruminants actually. Those are usually non-survival studies, but rather than actually using the non-survival techniques, our senior surgeon took laparoscopic biopsies of the liver sample, which is much less invasive and more comfortable for the animal, and that's how we reduced the number of animals that we use.

So it is possible to do it. You just have to have the innovators who are thinking about it and who are willing to. I love my surgeon, because he can be sitting there and you can absolutely distract him, just say to him, what is your next technique? And he'll be lost in thought. And then a couple months later you have a new technique going. It's brilliant.

That's actually how we did it. I think we were supposed to use around 200 cows for that study, and we did not use 96 of them because we were able to do laparoscopic instead of a more invasive or non-survival study approach.

DR. LANZA: I applaud that because I did bST tox studies over two years in cows. But the other thing I wanted to ask you, what about milk? Things that are going into milk, and that could be sheep, goats, cows. They're all being sold now. I saw camel milk on TV the other day, I didn't know it was possible.

DR. TAN: Okay, I don't have camels on campus. I have to be honest with you, I don't have those. But we actually maintain a herd of milkers on campus. So, we actually can spike the milk. We do that. We are also very much a part of the milk studies at FDA. So, yes, we do milk work too.

DR. LANZA: Thank you.

DR. GANEY: Thank you, again, and I think we will move on now to the Office of Regulatory Affairs.

Agenda Item: Office of Regulatory Affairs

DR. LINDER: Good afternoon. Thank you for the opportunity. I think I'm closing out the FDA portion of the meeting. I am Sean Linder, the deputy director within the Office of Regulatory Science, or ORS, within the Office of Regulatory Affairs.

I'll start with a little bit about ORA. We're a little bit different than the other components or centers of FDA in that we're really the field force that take the guidances and the rules and those types of things and go out and do surveillance and enforcement work. ORA has about 5,000 federal employees in total, and about 80 percent of those perform kind of the inspectional, investigation, compliance, sample collection components of what we do, and the remaining 20 percent or about 900 to 1,000 of us work on the science side of it within ORA's

Office of Regulatory Science. We do primarily the laboratory testing to ensure compliance with whatever rules of compliance programs that the centers provide to us to ensure the products are safe and effective.

Within ORA, this idea of performing scientific testing and having some research component of that has to have some framework. A few years ago, we set up our own science strategic plan and kind of set a list of core principles that we were going to abide by as we developed scientific evidence in support of agency enforcement actions. So, to that, all of our laboratories, we operate 15 laboratories across the United States, and I have a map on a subsequent slide.

All of our laboratories are accredited to ISO/IEC 17025 standards, which are the standards internationally recognized for testing and calibration laboratories. Work really hard to have an efficient but also strategic portfolio of things that we do, and part of that is to include laboratory capacity beyond FDA, so that end, FDA spends a large amount of money partnering with state laboratories, state public health laboratories, to fill in gaps, whether it be in testing, whether it be in participating in methods validation exercises. Those types of thing, to kind of get to that thing that you may have heard as far as the integrated food safety system.

We also kind of move outside of the typical boundaries of collect a sample, test a sample. We've in the last few years been working on rapid point-of-entry testing, and what that means is this is primarily for imports that are coming through ports of entry, through international mail facilities, these kind of nontraditional places to stop products as they come into the country, do some assessment of them scientifically, and then make an admissibility decision.

The last couple of years, we've deployed scientists throughout these types of locations on blitzes, and we'll have more of a permanent presence in the years ahead to test, again, products coming in globally into the United States for import.

In general, our lab methods and our lab capabilities are designed to be investigative. We participate in all of the outbreak responses, things you may have heard about in the news recently, like the EzriCare eyedrops, or some microbiological outbreak that's going on. Typically our labs are engaged with that, receiving the samples from the investigators in the field, analyzing those, and then trying to come some conclusion that is defensible.

We also do a lot of work with standardization of the way our regulatory testing paradigms are implemented

with those of other international counterparts. As an example, we're engaged in systems recognitions with other governments across the globe to look at are the way that we look at regulatory testing equivalent to what other government regulatory agencies throughout the world or their assessment schemes and their ways of approaching regulatory science; is there some equivalency there, and if so can we depend on each other to answer larger problems as they come up?

One of the things that we pride ourselves on that's a stalwart of ORA's regulatory testing is our timeliness and speed in decision-making processes. Most of the samples that we receive historically are imports. For those of you that are familiar with the import process, a product comes in, it gets detained, it sits while the agency does its work in the background. So that can cause financial stress points for importers or manufacturers as their product sits and waits for an admissibility decision by the agency. So we work really quickly to try to expedite that testing but maintain the quality and integrity of the product, and then work with our colleagues at the center to ultimately make that admissibility decision.

And then we also do a lot of work both foreign and nationally to look at lab capacity building. Most

recently we've sent sensory experts or people that smell fresh seafood products, fish, shrimp, other types of seafood, but they have an organoleptic trained nose where they can detect the odors of decomposition to determine the freshness of a product. That becomes really critical for those countries that export a lot of seafood products to the United States. We want to ensure that they're catching as many of those products that may be not fit for human consumption before it ever leaves their own country. So we've spent a lot of effort sending our own trained scientists with these kinds of expertises and organoleptic analysis to other countries to train our regulatory partners over there.

Just a quick kind of snapshot of where our laboratories are located. Fourteen of them, some of them are collocated, so ORA went through what's called a program alignment exercise in 2017, so as an example in Irvine, California, which is close to Los Angeles, we have a foods lab and a medical product lab. Structurally, managerially independent, but collocated in the same facility, so it's a little bit of funny math sometimes as to whether we have 15 labs or 12, but we have 15, just happens to be that three of them are collocated.

The photos are of a recent lab renovation project. The ribbon-cutting exercise for that is next

month, it's our Winchester engineering and analytical facility right outside of Boston, Massachusetts. We've been strategically modernizing our laboratory network across the United States for the last seven or eight years.

Kind of narrowing the focus here to kind of our research landscape, and again I said our ORA science portfolio was roughly 900 to 1,000 scientists and managers. Of that, we have a pretty small research portfolio. We may have ten or so FTE that are solely dedicated to research efforts, and another maybe 30 or 40 that do it as part of their job description, but not their sole function. So it's a pretty small landscape, but just to give you kind of an idea of what our big buckets of research, how we identify those, this slide kind of depicts different buckets, and then the number of research projects completed in each one of these buckets.

As you can see, we're not doing a lot of work in toxicology or risk assessment. We're doing it more in how do you look for a particular analyte, a particular pathogen, in a very complex matrix, whether it's a food or a dietary supplement, or maybe it's we're trying to answer some pharmaceutical efficacy question for an innovative versus a generic, to ensure equivalency or regulatory compliance. So it's a pretty large landscape of methods development type of activities, but very small landscape

when it comes to pure educational or risk assessment or trying to inform type of research projects that many of the other centers are more invested in.

We really look at outcome based metrics. It's a small portfolio, we want to be efficient with what we're doing. We want to have whatever efforts we put in have an output that they can be used to further the mission of ORA and FDA as a whole. So on the vertical lines here the headers are the impact categories, and as you go through the boxes they are the metrics that we can measure. If you just look at the far left, bring visibility to ORA science, how can you do that? The typical things you would see, posters, official methods, maybe those are compendial methods, publications of scientific articles or publications of LIBs; those are laboratory information bulletins.

If the agency is rapidly trying to solve a problem, a lot of times we will put out in the public space a laboratory information bulletin, which is our first pass at a method to solve that problem. You ask, well, why do you do that? It's maybe not fully vetted science, maybe it hasn't been multi-lab validated. We put it out there because typically these are emergency response situations, and what we generate with our own methods development oftentimes helps states or private labs or whoever else may

be trying to address that issue as quickly as we can. So it's just a rapid dissemination of information tool.

And then you go across the columns here. Increase our diversity, we're constantly working with the centers to try to solve new problems. Maybe it's new products, maybe it's new target analytes, maybe it's some outbreak that is a little bit different to us, as for example, Cronobacter. I think you all probably are very familiar with in the infant formula world.

So these are just kind of the tools in which we can put a metric behind to assess are the dollars, are the FTEs, are the capital expenditures for equipment or supplies, what do they really translate to on the other side? And this is all a new thing for ORA, to be frank. We stood this up in 2017 with that program alignment initiative that I mentioned earlier, which also coincided with ORA's first investment in standing up an Office of Research Coordination, which I'm going to mention just a little bit later.

This just gives you an idea, by the emphasis, the size, the font, of when we go out and do those assessments, we look at those outcomes and we tally the scores, where are we seeing the most bang for the buck? And a lot of times the larger font here indicates the larger metric. But we're adding knowledge to the knowledgebase, we're

doing -- SLVs and MLVs are single lab validations, multi-lab validations. We're maybe adding to surveillance program work. It again kind of ties into the idea of accountability for the dollars and hours that we put into these efforts.

I'm going to describe just a few more of the exploratory research, because I think we discussed earlier that a lot of our efforts are in methods development, and I said we do have a few kind of pure research, more traditional research endeavors, so I thought we would describe a couple of those projects for you.

The precursor here is the agency got some money back during the pandemic, the COVID pandemic, to assess supply chain issues, to assess product quality, to assess the potential for product integrity or efficacy, so ORA got a portion of those dollars, and we took some of those and really wanted to look at applied research in the ideology of a postmarket type of situation. So the first project, and we just funded these at the beginning of this year, the beginning of 2023. So they're just now getting started. The theme here is that we're working not only within ORA but within multiple centers of the agency to ensure that everybody's on the same page and the outcomes can be leveraged across different components.

The first project initiates here within Jefferson labs, which houses both NCTR and ORA's Arkansas laboratory, and it's to look at the quantitative analysis of lipid degradation products and cholesterol oxidation products in the lipid nanoparticle-based vaccines and therapeutics, and we've got collaborators from CDER, the Office of Pharmaceutical Quality, and CBER, the Office of Vaccines I believe, and then of course NCTR and our own scientists at ORA.

Kind of the takeaway here is as these products sit on the shelves, the stability, the shelf-life stability, some of these lipids and cholesterols can degradate and impact the efficacy. So the project really wants to look at what does that look like in the sense of product integrity and product efficacy over time and maybe even storage conditions?

This is an interesting project. As I mentioned, we've been looking more and more at ports of entry, and there's some 200-plus warning letters that the agency has issued just in the last couple of years, during the time of the pandemic, related to counterfeit or ineffective treatments, or adulterated products, that were claimed to treat COVID-19, or in some cases even other diseases. We want a portable toolset, right, so it's not always practical to collect a sample at a port of entry, send it

to a lab, do some analysis, wait for that to be done, and then make an admissibility decision. We want to be able to do some of these things that appear to be fairly straightforward right at the ports of entry.

So this team of scientists at our forensic chemistry center are really working on a specific handheld and/or portable set of tools to make some type of decision at the port of entry as the products are coming off the lines there with our colleagues at Customs and Border. Pull them aside, do an admissibility decision, and move on.

The final project I'm going to highlight really is looking at the integrity of gowns, and those of that are familiar with gowns, there's different levels of 1, 2, 3, or 4; and level 4 gowns are really supposed to be able to be resistant to things as small as viral particles, nanoparticles, something like that. These are regulated by the Center for Devices and Radiological Health, and we have done some work in the past with them on biological fluid penetration of surgical gowns and things.

This is going to be looking I think at a simulant of such, a simulant test article, to COVID-19 using some type of similarly-sized nanoparticle to see if they can assess the resilience of that gown to penetration of these particles.

I'm just going to finish up with a couple of things that ORA and NCTR have collaborated on in the past and collaborate still today.

This has been mentioned I think by several of my colleagues at FDA. There's a multitude of agency-level committees in which there's stakeholdership from multiple components. So we work and are involved in many of these committees and participate with our colleagues from other centers as well as NCTR. I don't think I need to necessarily read those to you.

Some historic things that we've done with NCTR and things that we're still doing today, and first and foremost, and very relevant right now, is the idea of C. bot and C. bot toxin and the mouse bioassay. NCTR continues to help us with a colony of mice and the facilities to house those mice, to test when we have products that are believed or suspected to contain C. bot toxin. We are, as well as many other people, working on alternate approaches to that, but currently the gold standard is still the mouse bioassay for that, and with all the attention right now with powdered infant formula, we are seeing quite a few consumer complaint samples in which clinicians or other evidence suspect that C. bot may be a component of whatever illness was observed, and so we have been receiving quite a few of these samples over the last

six or nine months. We appreciate NCTR's continued collaborative partnership with that particular program.

A few of these other examples really get to the data metrics, pattern recognition, artificial intelligence domain. I think that resides in Weida Tong's group. And the idea is that we look for things like bug fragments, bug parts, that's called the filth program within FDA. Believe it or not, there's tolerable levels of insect parts in the foods that you eat. But there's a way to think about it -- if we could train a computer to identify those parts as opposed to a human looking through a microscope for an hour trying to find those. So I think there was some success out of that, but the challenge is when you lay out the multitude of insects that are out there and the different species and subspecies, it's almost an infinite number, along with then the matrices that accompany those -- all the different food products -- it's a very complex equation.

But nevertheless, we've worked with NCTR in that domain, as well as algorithms to look at really complex analytical data coming off of mass spectrometers when it comes to persistent organic pollutant chemicals. Those of you that are familiar with that space, things like PCBs and dioxins have very complex response patterns when you look

at the data off a mass spec, and it takes a lot to deconvolute that and make sense of it.

I'd like to highlight two of the -- NCTR was really pivotal in helping us develop a pilot for what we call ALIST, which is an automated laboratory information system, and the idea here is we wanted to automate the work product that comes out of ORA's laboratories, and we had tried some other commercial off-the-shelf products. I wouldn't say it was overly successful. We worked with our colleagues at NCTR, came up with the pilot. It was received rather well.

And then the agency as a whole looked at it and said, well, we can't continue to that kind of internally, we have to go out find a contractor to carry this from the idea of pilot to full implementation. But nonetheless, without NCTR's help in that space, I don't know that we would have been successful as we are. Now we're approaching I think our third module of implementation of that, which will encompass somewhere in the neighborhood of 40 to 50 percent of our program work will now shift from manual, human writing or human typing, to an automated platform that becomes an electronic version or electronic records. So that's an important one.

And then we've also had some, I mentioned the import stuff at points of entry -- we had some discussion

with NCTR about are there ways to use some of the catalogues of information to spot counterfeit pharmaceuticals as they come in through these points of entry? Not only the pills themselves, which CDER has all the data on what a pharmaceutical should look like, from imprinting to color to size, to so on. But not only that component of it, but the packaging, the labeling, the colors. We could show you that as an example, you expose packaging to different types of light, and you can easily pick out an innovator or an authentic product versus something that's counterfeit because there's a standardized way in which the packaging is prepared and printed. Could AI tools or machine learning tools be advantageous for us to make quick determinations of counterfeit products? So more to come on that.

I think I mentioned we still work with NCTR in the nanotechnology realm here at Jefferson labs. It's been a decade-long or more endeavor. I still value that and want to continue in that space. And then I mentioned a couple of things about AI and machine learning that are important to us, but I think in the future, too, you think about the ORA labs and describe how big it is -- we're talking about tens of thousands of samples a year -- is there a way to harness the data that's coming out of some of these systems more strategically, and then make --

prediction is maybe a bold statement -- but could you find chemical or microbiological sensors there that may help drive the next generation of potential issues, whether its chemical contaminants or otherwise?

As an example, would we have known PFAS was an issue sooner? I don't know. But could that data somehow be harnessed and looked at more strategically? So we may at some point want to engage with NCTR on those types of projects.

Just to finish up, as I mentioned, in 2017 we stood up program alignment that created ORA's first research dedicated office. Selen Stromgren is the office director. I'm actually standing in for her today, she's on leave with spring break, I think, with her kids. But it's exciting. She does really well with the office. I know that she's worked within the Office of Science, the Office of Research, with the other FDA Centers and NCTR, and we're happy to share a campus here and find NCTR to be great colleagues in the space here.

With that I'd like to close, and I'll answer any questions.

DR. GANEY: Thank you, Sean. Are there any questions for Sean? I think it's growing late in the day. Appreciate that informative presentation.

We are now at breaktime. I've had a request to make the break only 10 minutes, so if we could all come back at quarter past the hour, and we'll hear from three of the divisions and then we will break until tomorrow.

Thank you, everyone.

(Break.)

Agenda Item: NCTR Division Directors: Overview of Research Activities

Division of Biochemical Toxicology

DR. GANEY: Okay, we are resuming, and we are going to hear from Dr. Beland about the Division of Biochemical Toxicology.

DR. BELAND: Thank you. I am Fred Beland and division director for biochemical toxicology, and I'd like to spend a few minutes just giving you an update.

There's a few slides we've been asked to present so we can compare across the divisions. The first one is the number of personnel in the division. We have 39 full-time individuals. There are 29 research scientists, staff fellows, and visiting scientists. Visiting scientists are typically people who are here, foreign scientists on J1 visas or H1B visas. So these are people with PhDs, typically.

We have nine support scientists. These are generally individuals who have bachelor's degree or

master's degree. We currently have one administrative person.

Weida was mentioning how many outstanding people they're trying to recruit. We're actually doing pretty well. We're short one support scientist, which the job announcement will go out in the next week or so. And we're short one administrative person because these are both due to requirements, and the job announcement is out, and I really don't anticipate any problems filling the position.

We don't have any graduate students at the present time. We have five ORISE postdoctoral fellows. These individuals are all supported by external funds. By external funds I mean non-NCTR funds, so Office of Women's Health, Office of Minority Health, and so forth.

I'm reluctant to fund postdoctoral fellows with NCTR funds just because we really don't know from year to year what our funding is going to be, so we've developed a model where if individuals want to have ORISE postdoctoral fellows, they have to secure outside funding.

So we have a total of 44 staff members. One thing that would really, I want to compare to what we had, say, 10 years ago, what's missing from this mix are true visiting scientists, people who come here for a short period of time. Part of this is due to the pandemic that we've all suffered, but the other is it's very difficult to

bring in foreign scientists for short periods of time. I've mentioned this before, and it still hasn't changed.

There are two major changes that I'd like to emphasize here. One is it's been suggested for quite some time that I have a deputy director. There were various reasons why I could not do that, but these finally got resolved, so we put out a job announcement, and of the people who applied, Luisa Camacho was clearly the most qualified. Luisa is really a true pleasure to work with. What's really important, she understands where the division fits both within NCTR, but more importantly within the FDA.

Another major change is Woody Tolleson was a senior scientist within the division. He retired, and this allowed us to go out and recruit another senior scientist. One of the suggestions the Science Advisory Board had made for a number of years, was to increase or develop our expertise in, say, immunotoxicology or immunology. So that's where we focused, and we were fortunate enough to be able to recruit Tariq Fahmi, who was already supported by the Offices of Women's Health and also Core, so he was able to bring a postdoctoral fellow with him, and the one support scientist we're currently recruiting will work in his laboratory.

This illustrates that we really do collaborate with other divisions at NCTR. As Tucker Patterson pointed

out today, the center has 500 people, so in order to increase our productivity, it's really a great benefit to collaborate. We also collaborate with each of the product centers. In addition, we have collaborations with other federal agencies. For many years we had a lot of support from the NIEHS. I'll talk a little bit more about that later. Igor Pogribny gets funding from the National Cancer Institute, Luisa Camacho has great interactions with NCATS and NICEATM. Our modeling group has interactions with the EPA. Camila Silva through her work with COVID has interactions with CDC.

We also are involved in international organizations. For a number of years, a number of us have been involved in IARC monograph reviews of the carcinogenic hazards of chemicals. IARC is part of the World Health Organization. Luisa Camacho is involved with various (inaudible).

The mission of the division really hasn't changed. Whereas other divisions, they've talked about a lot of turnover, we're actually a very stable as far as personnel and we're relatively stable as far as what we do. We conduct fundamental and applied research designed to define the biological mechanisms of actions underlying the toxicity of FDA-regulated products.

To be more specific, we characterize toxicity and carcinogenic hazards associated with chemicals, specifically those of interest to the FDA. Traditionally, the way we've done it, and still do it to a great extent, for many years we've received an extensive amount of funding from the National Toxicology Program to conduct bioassays. These are on chemicals that the FDA had nominated for evaluations.

Over the past few years, partly due to a change in leadership with the NTP, the funding has dramatically decreased. Nonetheless, we still are doing some bioassays that I'll describe later. We continue to conduct mechanistic studies. These involve animals, but they also involve in vitro studies. And then we take the bioassay data, the mechanistic data, and we have a group of computational modelers. Currently we have six individuals who use these data, use the animal data, use the mechanistic data, and then try to do extrapolations to humans.

As far the metrics go, through the years that I've been at NCTR, this I think has gone through -- we've evolved. Currently, and I imagine it's going to continue to stay this way, our major output is what we give to the product centers. This tends to be reports. For instance, Suzy Fitzpatrick mentioned that we had worked with 6-2-

fluorotelomer alcohol. During the last year, we conducted the studies, prepared a report. This was furnished to CFSAN. Likewise, she also mentioned that we were working with tattoos, and again, during the last year we finished studies. We prepared a report, and this was furnished to CFSAN.

With regard to the NTP, we're just completing a report on dermal application of triclosan. Dana van Bemmel mentioned that our work with CTP where we've have completed projects on the tobacco-specific carcinogen NNK. We have reports, these were furnished to CTP. We're in the process of furnishing reports on nicotine, primarily nicotine pharmacokinetic studies.

So the reports are turned over to the product centers. Once the product centers are happy with the reports, then these data can then be converted into manuscripts. But the process is, we don't publish the manuscript until the product centers are happy with the data, are completely comfortable, because we don't them blindsided as to what we're doing. Nonetheless, as far as manuscripts go, we are I believe quite productive. Last year we had nearly 40 publications done by people within the center.

What I would like to do now, I just want to talk about three areas. And what I want to do is primarily

emphasize where we're going. I need to talk a little bit about what we've done, but these are studies that we really have not started yet. I'm going to tell you what we haven't started, and then we're seeking advice both from the Science Advisory Board, but we're continually seeking advice from the product centers. Is this what they need? Because if we do something and they don't need it, we've wasted our time and money and so forth.

We're going to do it with tattoo pigments, we're going to do a cannabidiol, and finally we'll talk about nitrosamine.

Last year, when we met, I talked about tattoo pigments. The principal investigator on this study is Svitlana Shpyleva, and this study is done in collaboration with and with funding from CFSAN. As Suzy Fitzpatrick mentioned, tattoo pigments are considered cosmetics. Cosmetics are now under the Office of the Chief Scientist. But I still consider it CFSAN. Anyway, the important point here is that as everyone should be aware, tattoos are very prevalent in the United States, and also, for that matter, worldwide. The primary group are rather young people, and amazing is that a very high percentage of women.

What people don't realize is that tattoos contain a lot of material. The typical tattoo is 250 milligrams, average. Thirty percent of the population have four

tattoos. So they could have up to a gram of the pigment put in.

Another thing that's not recognized is the amount of pigment at the tattoo site really decreases. I was quite surprised about this. Since there's a very high rate of tattooing and women of childbearing age, it was possible that the pigments are going to -- since they decrease as it goes, it could get into the fetus and this could cause possible health problems.

When I spoke last year, I talked about where we had tattooed mice, and I showed the results, and one of the things that we noted is, as I mentioned in the third bullet, we knew how much we were putting on the mouse, and if you looked at the site of tattooing, the decrease was greater than 90 percent. The problem was our first data point was two weeks after the tattooing. For a number of reasons, we did not consider the mouse to be a very good model, and so we started looking for a second model that could be used.

What we were in discussions with CFSAN about is the use of minipigs, and specifically Yucatan minipigs. The way we intend to do this study, and again, this is where we stand at the moment, is we're in discussions as to the types of pigments and what the specific steps will be. We have a draft protocol that's being reviewed by

colleagues at CFSAN. We initially intended to start with pigment red 22, which is carbon labeled. We have this on hand, we're comfortable working with it, because this is one of the compounds that we used on the mice. During our discussions with CFSAN, they have highly recommended or suggested or encouraged that we work with carbon black. This is a relatively recent suggestion. We really do not have any experience working with carbon black.

The other problem is that you really can't make carbon 14 carbon black. We have come across a procedure for making it tritium-labeled, and looks actually that it might work quite well. So our current intent is to use both, in separate animals, of course, pigment red 22 and carbon black. And the way we will do this is we will initially start with ex vivo. We will have pig skin that we will develop the techniques for tattooing, the size of the needle, how much pigment can we get in, the actual pattern that we'll use on the skin. Once we are comfortable with this, then we will move to a live pig, and we will see how much pigment we can get in on the dorsal region of the Yucatan minipig.

The second step, we really don't need to use radioactive material for the pigment red 22, because we can excise the tattoo, extract the pigment red, and quantify it by UV. That will not work with carbon black, so I

anticipate we would have to use tritium-labeled carbon black at this stage. But once we get an idea of how much -- and what we're doing is we're aiming for the amount of pigment that you would find when a human is tattooed, which is around 3.5 milligrams per centimeter squared.

Once we are comfortable with the live animal, then what we want to do is to investigate the systemic distribution. We want to know when the peak level occurs in plasma after tattooing. This will require radiolabeling the material.

This is the first steps that we would have in an initial proposal. Once we have completed this, the subsequent studies would be to then, we would take the time of the peak levels in the plasma and investigate the biodistribution in organs and tissues. I'm saying pregnant Yucatan minipigs, but the initial study probably would not involve pregnant animals.

From the mouse study we know there was a decrease in the skin, we could find the radiolabeled pigment red 22 and the other pigments that we worked with in adjacent lymph nodes. We could find in the liver and lesser amounts in other tissues. But again, remember, we were measuring two weeks after the tattoo, and I have a feeling that things occur much quicker than that.

Once we've established that, then our plan would be to see whether or not we would then work with pregnant Yucatan minipigs to see if there's transfer to the fetus, after tattooing.

Tucker Patterson, in the initial talk this morning, and then also Suzy Fitzpatrick, mentioned cannabidiol, as I did last June when we talked. Our emphasis on cannabidiol is first of all because it's a drug. So the Center for Drugs evaluated it, they approved a drug called Epidiolex. There has been a lot of use after the 2018 Farm Bill. It's now in a lot of products. You can go into drugstores and see everything containing CBD.

Suzy Fitzpatrick mentioned that it's in cosmetics. And we don't know if it's absorbed through the skin and systemically distributed. There's been reported adverse effects on the liver, and there's also been effects, potentially, male reproductive toxicity.

When we talk about cannabidiol, we need to talk about its metabolism. The left-hand side of this slide shows cannabidiol, it undergoes oxidation, cytochrome-P450 catalyzed oxidation, to 7-hydroxy cannabidiol or CBD. And then you get subsequent oxidation to 7-carboxy-CBD, presumably through an aldehyde. There must be a secondary oxidation with aldehyde that we don't see in the assay.

Suzy Fitzpatrick mentioned that we had done some CBD pharmacokinetic studies. The principal investigator for this is Qiangen Wu, and we have funding from the FDA Cannabis Product Committee.

What I'm showing here is the species, dog, rat, and so forth, mouse, males, and females, and I'm showing the percent distribution of CBD, 7-hydroxy-CBD, and 7-carboxy-CBD. The first three, the dog, the mouse, and the rat, these data come from preclinical studies that were submitted by the drug company when they were applying for the approval of Epidiolex. And if you notice, with the dog, CBD was the major plasma metabolite. In the mouse, and again, the males and females behave the same. Males and females in the mice behave the same. And it's pretty well an equal distribution of all three, the drug and the two metabolites.

In the rat, CBD is the major metabolite -- it's not a metabolite, the major product detected. Very little hydroxy and quite a bit, 30 percent, 7-carboxy.

The problem is, the issue raised by the reviewers at CDER was that if you look at humans, humans the major circulating metabolite is the 7-carboxy. It's almost, it's 97 percent of what they see. And the issue is, if you're trying to establish if there are toxicities associated with CBD, is it due to the hydroxy? Is it due to the carboxy?

And if it's due to the carboxy, these animal species, the dog, the mouse, and the rat, really are not a good model for humans, especially if indeed the 7-carboxy -- we need to know is the 7-carboxy, is that a true toxin metabolite?

Last fall, we thought that one way to address this was to use rhesus monkeys and see whether or not rhesus monkeys gave a metabolite pattern that was similar to what was observed in humans. So we set up a study and have completed the dosing and the analytical work, and as you can see toward the bottom of this slide is that the monkey is really not a very good model. It's a good model for a rat, but it's not a very good model for the human.

We know from the literature that rabbits seem to behave like, give a metabolic pattern like humans. The problem with what's reported in the literature, it was only done in female rabbits, and the female rabbits were pregnant, so it's possible that there's a sex difference. It's also possible that this pattern is due to the fact that the animal is pregnant.

So what we're going to do, and we've received funding to do this from this Cannabis Product Committee, is we are going to treat rabbits, male and female rabbits, to examine the metabolic pattern. If indeed this pattern is reproduced, then this will give us an animal model that we can then do other investigations regarding toxicity.

This slide was presented by Suzy Fitzpatrick, but let me just repeat it. In addition to in vivo studies with CBD, we're also doing in vitro studies with CBD, and the principal investigator here is Si Chen, and with funding from CFSAN, done in collaboration. Again, all these studies we interact very closely, we discuss what we're doing, we discuss the results, we're discussing where we're going.

What Si and her colleagues have been able to determine is that -- and this has to do with male reproductive toxicities -- that CBD and its main metabolites, and the main metabolites I'm talking about the 7-hydroxy and the 7-carboxy, can inhibit cell proliferation and decrease DNA synthesis, in mouse and human Sertoli cells. So the comparison, we knew that there is data that CBD was a reproductive toxicant in mice, and we want to see do mice and human cells behave the same, and this was published -- the lead author on this is Yuxi Li, who's a postdoctoral fellow with Dr. Chen.

And then they also established that CBD disturbs various interrelated signaling pathways and cellular senescence in primary human Sertoli cells. And again, this has also been published. They have additional data that indicates that there's the induction of apoptosis in mouse and human Leydig cells, and they've also found that 7-

carboxy is less toxic than CBD, while 7-hydroxy is similar. These data are in the process of being written.

In addition to being, as I mentioned right at the beginning, instead of -- CBD is suspected of being a male reproductive toxicant, but it's also a liver toxicant. This is where Si Chen and her colleagues -- her colleagues are Dr. Lei Guo and also Yuxi Li, and Xiaoqing Guo. And the idea is that liver safety concerns have been reported in many patients after oral administration of CBD. The causal underlying mechanisms of liver toxicity are largely unknown. And furthermore, there's been no evaluation of the two metabolites, or the role of specific cytochrome P450s in CBD-induced liver toxicity.

This is what they proposed -- these three individuals work as a work and they're very productive -- is to evaluate the cytotoxicity of CBD, 7-hydroxy, and 7-carboxy in various human live cells, including primary hepatocytes and HepG2 cells. I'm showing the endpoints that we measured, reactive oxygen species, cell cycle alterations, mitochondrial dysfunction, apoptosis, autophagy, ER stress. These are measurements that they have made in a number of different cells.

They also have transected HepG2 cells with specific cytochrome P450s, so they're going to use this panel of cells then to establish what cytochrome P450s are

responsible for the metabolism of CBD. They have a panel -- I figured it's greater than 10 individual cytochrome P450s.

This is where we stand with this particular protocol. They have a concept paper that has been submitted for review, assuming that -- and then hopefully funding will come -- first of all, we have to make sure that CFSAN and CDER are comfortable with what we're proposing to do, and hopefully funding will then follow.

This is the third study, and this was touched on earlier today by Dr. Clingman when she gave the overview of the Center for Drugs. The alkylating agent ethyl methanesulfonate has been detected as a contaminant in the preparation of certain drugs. She talked about nitrosamines in general, but the initial concern dealt with EMS.

EMS is clearly carcinogenic. There's no question about that. However, the dose response data are currently not available. Dr. Clingman mentioned, and I suspect that Bob Heflich when he speaks about genetic and molecular -- Division of Genetic and Molecular Toxicology, he will also talk about just nitrosamines in general. But what CDER really would like to have, the data they currently have available is mutagenesis data, and they really would like

to have carcinogenicity data, and they need these data to prepare what we'll call a meaningful risk assessment.

What we're proposing to do is to conduct a bioassay, and then we're going to combine that with the anionic data and the mutagenesis data, and then this will provide a comprehensive foundation to establish the risk to humans from exposure to EMS, and then perhaps by extrapolation to other nitrosamines.

I'm going to be the principal investigator on what we'll call the EMS bioassay. This is done in collaboration with investigators at CDER. Where we currently stand with this is I have a draft protocol that I've sent to the Center for Drugs for their -- it's at the proposal -- this is the first idea of the way we should go about.

As I mentioned, EMS is carcinogenic. That's not the question. The question is, what is the dose response look like? What I'm proposing to do is I'm going to restrict the study to a single species and a single sex, because that's what we're interested in, and if you look at all the animal data, it seems like the most sensitive species and sex is the female Wistar rat. They develop on exposure to EMS, develop mammary gland tumors.

As far as the dose range that is shown here, the highest dose, 30 milligrams EMS per kg per day, is what was

used in a bioassay conducted by a Japanese group. So I will clearly cause mammary gland tumors. The lowest group of the 0.3 milligrams is what was the point of departure from the mutagenesis study conducted by Xuefei Cao and Bob Heflich, so I'm spanning the mutagenesis range to a carcinogenesis range.

Based upon what I'm projecting is, I know from a background level what I should get from spontaneous tumors, and I realize this is a lot of animals, but if we're trying to define a dose response, you really do need a lot of animals. This, using 150 animals, I should be able to detect a 10 percent increase over background, at the low dose. And likewise, I can detect about the same using 50 animals per dose group at the high dose.

So this will be a two-year study, it will be a gavage study, a daily gavage study, and it'll have all the appropriate controls. EMS, we will measure stability of EMS, and so forth.

There will be a second study, and this will be -- there's mutagenesis data that has been conducted by industry, and also by Bob Heflich and Xuefei Cao. What we really don't have is DNA adduct data now. And I think this is important, so this is going to be the principal investigator for this is Jia-Long Fang. Again, this is in collaboration with CDER. What we want to do is to

determine what the DNA adduct profile is in rats administered EMS, but instead of using just straight EMS, we're going to use deuterated EMS, and the advantage of this is we will then be able to determine what DNA adduct formation from the drug, as opposed to endogenous DNA adduct formation, which occurs.

So we will measure d-5 ethyl groups added to the DNA, but we'll also measure ethyl groups that come from endogenous process, and we'll also measure methyl groups that come from endogenous process. We will quantify DNA adducts as a function of dose and time. With other carcinogens we typically get to steady state adduct levels in about 1 month, and in addition to doing the DNA adduct data, we're going to do Pig-a mutation frequency.

You'll notice that the doses are going to be identical to the ones used in the bioassay. So what we'll do is the package we will present to CDER will have carcinogenicity data and we'll have DNA adduct data, and we'll have mutation data from this experiment, and we'll also have mutation data from previous experiments. And we're hoping with this entire package that it will be comprehensive enough that we'll be able to come up with a good dose response and also that will allow them to do a good risk estimation.

This is the end of my talk. There's one last thing, it's that I hope in the future we can do this in person. I'm tired of -- I think we're past the pandemic far enough that we should give serious thought to holding these SAB meetings in person, because I think it has a distinct advantage over doing this online.

Thank you.

DR. GANEY: Thank you, Fred. I have a quick question for you, and then I'll open this up for others. My question is, your primary human Sertoli cells, do you know if they metabolize CBD to the 7-carboxy form?

DR. BELAND: I am not certain, but I don't think they do. I would prefer to check with Si Chen about that before I say that definitively, and I could shoot you a note.

DR. GANEY: I was just curious. Let's just say that they don't, let's just hypothesize that they don't, like you think they might not. Does that tell you anything about the importance of that metabolite for the toxicity?

DR. BELAND: You could have hepatic metabolites in circulation to the Sertoli cells.

DR. GANEY: Well that's true. Okay, thank you.

It looks like John-Michael might have a question.

DR. SAUER: I do. Great work. It's been interesting watching your advancement over the past couple

of years. I have a question also about that 7-carboxy-CBD. Does it undergo secondary metabolism by either glucuronidation or by amino acid conjugation?

DR. BELAND: Qiangen Wu is looking for glucuronidation right now. This is in the in vivo samples. One problem we run into, it doesn't seem to be that stable, for reasons that we don't understand at the moment.

DR. SAUER: Interesting because I was just wondering about a phase II bioactivation --

DR. BELAND: I know. Because I was always concerned because we don't know that maybe we're just looking at very minor portion of the material, most of it's glucuronidated. But at the moment we don't know.

DR. SAUER: Okay, great. And then just a quick question about the tritiated carbon black. I'd like to make sure that's not exchangeable, right?

DR. BELAND: I just discovered this about two weeks ago, and I need to think about it a lot. I searched what I thought was quite thoroughly, and I can only come across one paper, and what they did is they used it do exchanges with some rubber material. What I'm thinking of, first of all, tritiated water is really cheap, so I can do a lot. I will set it up, and it's something we can do in the lab, which is kind of nice. I don't have to send it out, I don't have to work with tritium gas or anything like

that. But I'll start working at low levels and just see what happens. I think it could be kind of fun, actually.

DR. SAUER: Maybe it could yield something very interesting.

DR. BELAND: It's quite clear that I can't work with carbon, and that's what these people -- the paper dates from the late 1960s, and that's what they pointed out. There was no feasible way. But as far as the synthesis goes, it's really simple. You basically throw an acid and cook it for a while, then just start washing it, so you get down to constant activity.

DR. SAUER: Great. And I do agree. It'll be nice to get back to non-COVID environment, and get together, because I think we could have a really nice discussion at dinner around your EMS project. So thanks a lot for everything.

DR. BELAND: Yeah, the thing is, people are now going to the SOT meeting. I've been at the ACS meetings. I think we need to get beyond this fear and try to get back to a bit of normalcy.

DR. GANEY: Are there other questions for Fred?

I also share your desire to get back to in-person meetings. Thank you, I guess we'll move on now to Weida will tell us more about the Division of Bioinformatics and Biostatistics.

Agenda Item: Division of Bioinformatics and Biostatistics

DR. TONG: Again, my name is Weida Tong. I'm the division director for the Division of Bioinformatics and Biostatistics.

This is just disclaimer.

The division has very much remained the same, at least four the past several years, and we still have the four branches, and both bioinformatics and biostatistics branch, with folks on the regulatory science research. Research-to-review branch is try to take that research outcome to for the regulatory applications. The Scientific Computing Branch basically is the centralized IT resources to supporting entire NCTR. And under my immediate office, we also established a special team called AI research force team, which is focused on AI for the FDA. And as you already know, our division was reviewed last year, and so since then we have a couple people left the division. We also are bringing in a couple people. So overall speaking, you have very much the similar number of FTEs, and on top of that, we have around 10 postdocs and plus five graduate students.

Our vision, mission, and goals also are remain the same, and we are trying to make the division as an indispensable resource to FDA. For that, we try to be sure

everything we do has some relevance to the FDA regulatory mission. As such, our linkage with the product centers continues to be strengthened and our capability evolves to meet the current and future needs of FDA.

Our specific goals is to apply in silico approach, including artificial intelligence and bioinformatics and biostatistical methodologies, as well as computational modeling, to focus on the areas which are important to the FDA.

This slide just summarizes some of the longstanding collaborations we have with other FDA Centers, and the first is from CDER. I have the next slide to explain to you about where we are for this project. Dr. Sean Linder already mentioned about ALIS with the ORA, and the ALIS project is we've been doing that since probably 2019, which basically is an automated laboratory information system to manage the laboratory data generated from ORA laboratories across the countries.

As Sean mentioned, our role is really prototyping various modules, and now the ORA bring these modules into the production level. Officially, we already concluded this collaboration with ORA.

Another project is with CTP, and Dana already mentioned about ASSIST4Tobacco. This is an AI-based information retrieval system. This year also marked the

end of this project, but there is a lot of discussions between the CTP and our group, and likely we are going to expand it this project for another several years, and I hope I can come back next year to explain to you about the new objective and expansion of this project.

This is just giving a quick update for the three CDER projects, because we've been working on it for about 10 years now. On the right side is about FDALabel. You heard that these tools have bene mentioned by numerous people. And at bottom right, it's the pie chart which shows how many people from the various FDA Centers participated in the training, FDALabel training, in the last year. And on the top right is the bar chart indicating between 2016 to 2022 how many users increased over that time.

Before I leave the FDALabel, I wanted to mention that this project that there was a managed by the Office of Scientific Coordination under the leadership of Dr. Hong Fang, and our division just provided the technical support to this project.

On the left side, at the left top, is the DASH project. The DASH is the software tools to manage the lifecycle of a drug starting from the IND submission all the way until the NDA application, and we have been developing bells and whistles for these tools for many

years now, and last year we completed another DASH-like system to support FDA's Safety Policy Research Team. This system actually was separate from DASH, but eventually it can be incorporated into the DASH environment.

In the bottom left is about the smart template systems. In the FDA, in the CDER review process, normally the reviewer is following some sort of a template, and those templates are the same how it's structured Word document. So the reviewer put the content and the text into the different section of the template, and then convert to a PDF file and upload it into the database. It turns out that's very difficult to find the information in the PDF. So what we did is we did not change any of the template, it has the same look, same feel, but once the reviewer puts the information into this document we have the database behind it to suck this information into the database, to serve as institutional memory. So we call these a smart template.

We started this project with one template, which was used by the pharm tox, now we have already 13 smart templates that have been developed, and we will have more smart templates to go. We also have close to 1,900 review documents that are available from the smart template system. When the data is submitted to CDER, particularly IND submissions, always with the submission always come

with the study data, and those study data were formatted using the SEND standards, and then stored in the separate database called the Janus database.

What we did, we created a link between the smart template systems to the Janus database, so we will be able directly to access these study data, to the Janus database. And we also have about 2,00 protocols and meeting minutes uploaded to the smart template system right now.

In 2022, reviewers have logged into the smart template system over 23,000 times. The templates also have been downloaded over 14,000 times, and we also have over 500 review documents that were uploaded into our system. So truly this system has become widely used in the CDER review process.

In the last year, on the smart template system's team, and including both the reviewing scientists from the CDER side as well as the scientists from the Office of the Scientific Coordination, and our division, received the FDA-level award for this collaborative work.

Along with this award we also received two additional awards, both are related to the SEQC2 consortium efforts. One is the group award; another one is for the paper published in Nature Biotechnology.

I would like to take a pause here just adding a little bit more information about the distribution in our

division. If you look at the senior scientists versus junior scientists in our division, and we are about 1-to-2 ratio. But in 2022, I'm pleased to see the junior scientists have really stepped up and played an important role, not only in conducting research but also to support FDA Centers.

In 2022, we have two new projects that were initiated and the first one is part of the AI4TOX program, and more specifically is about SafetAI. SafetAI actually was initiated by CDER collaborators, and they want us to develop AI models for five important endpoints in the drug review process, and these are: liver toxicity, carcinogenicity, mutagenicity, cardio-tox, and kidney toxicity. In the last couple of years, we already published the models for the liver toxicity and the carcinogenicity, and last year we focused on the mutagenicity, and more specifically it's about Ames test results.

On the right side is the model and procedures, and I already explained how we use the deep learning method to develop these predictive models, we call DeepAmes, for mutagenicity.

We compared DeepAmes against the five commonly used machine learning methods, including KNN, the linear regression, supportive vector machine, random forest, as

well as XGBoost. And we looked at prediction accuracy as well as applicability domain, and you can see from the right side that DeepAmes performed better compared to other five commonly used machine learning methods, and we really hope DeepAmes can provide alternative tools to assess the mutagenicity, and not only just for drug development, but also to support the drug review.

At this point we are trying to establish a secure environment in CDER to implement this model in this environment to provide prediction to the drugs, particularly drug impurities, during the review process in terms of the mutagenicity.

The second project we started in 2022 is in the bottom left and shows here is to develop AI tools to handle to mining the CDER science and the research investments tracking archive, called SARITA systems. And this is a natural language processing project folded into the BERTOX, one of the initiatives we have under AI4TOX. This project also is handled by our junior scientist, Dr. Ting Li.

SARITA system has actually been for a long time in CDER, and mainly they captured research activities, including publications and research projects, as well as intramural funding. However, the information in SARITA is not entirely completed. What we are asking to do to first of course complete all the information, particularly in the

publication side, and then we are going to apply the AI to mining to group them into different research priority, and then CDER's senior leadership will be able to align these research areas with regulatory priorities in CDER. This is an ongoing effort, and we already completed two components, and one is publications, another one is CDER projects.

Just to continue my praise of the young scientists in our division, last year we heard about the Bioinformatics Challenge, which was organized by Environmental Mutagenesis and Genomics Society, and so we decided to enroll in this competition. Dr. Ting Li presented the work related to SafetAI, and Dr. Xi Chen presented work related to the AnimalGAN models. Turns out that both of them actually have been awarded first and second prize, and I'm extremely happy with their performance.

Also, you heard about FDA Intramural Grant applications. On the right side you see we have five categories of the grant mechanism, the Chief Scientist's challenge grant, medical countermeasure initiatives. Another two grants, one was organized by the Office of Minority Health and Health Equity; another one is administered by the Office of Women's Health. The last one is a collaborative opportunity for research excellence in science.

I think starting next year, the last one is going to be incorporated into the Chief Scientist's challenge grant, so starting next year, we only have four.

As I mentioned in the last year, we have four projects funded in 2021. They all started, the official starting dates are 2022. In 2022, we also had three projects get awarded, and two were awarded as a new project, one which is an extension from the 2021 project.

I just wanted to emphasize, for this year, two new projects again were handled by the junior scientists in my division, and one is by Dr. Leihong Wu, and this project was funded by Chief Scientist challenge grant. Another one is by Dr. Wenjing Guo, and her project was funded by the Office of Women's Health.

In the next three slides I'm going to provide a little bit more information for one of the projects, which we just got. That's by Dr. Dongying Li, and she wasn't here, and this project was awarded by the Office of Women's Health last year.

The project title is investigating early signs of sex differences in adverse drug events to better protect women's health. The project was in collaboration with other divisions in NCTR, including DBT and DSB. And we also have a collaborator from the Office of Computation Science as well as the Office of New Drugs from CDER, and

we already hired a new postdoc to start this work. The project duration is between October 1, 2022 to September 30, 2024.

So to just give you a little bit of background on why we want to look into this particular sex bias issues related to drug adverse events. Now, it is well-known that drug adverse events has been observed more in the females than males. There is a lot of explanations, but the jury is still out there. But the prevailing theory is the difference in physiology between the male and the female, which play a significant role in drug metabolism. There are also hypotheses. For example, the BMI and it is commonly believed that females have a higher BMI compared to males. That means the drug is going to stay a little bit longer in the female than male, which is going to result in more drug interaction to lead to the adverse events.

Also, clearly the female is much willing to take the drugs. They have a much higher self-awareness to taking care of the wellness of their body. The last one I'm not sure this is correct, and they also think the female have less pain tolerance. That's why once they have a little bit more pain, they are willing to take more drugs. I don't know whether this is true or not, because if anyone can sustain the birth pain and sustain any kind

of the pain. But you can see the point of this, there's a lot of theories out there, but our project is not try to get at the bottom of it and to understand that what particular reason or the mechanistic level to understand why existing sex difference between the male and the female.

So what we wanted to do is we are asking the question. If there is a sex biased events happen in the preclinical space, does that have any relationship to the clinical setting. So that's what we are trying to do. We are going to play a lot of statistical tricks, but at the same time, we also are going to implement the experimental procedure for the validation.

So the strategy actually was divided into two parts. The first is a focus on hepatotoxicity. We already selected 10 drugs which we know to exhibit the sex bias effect in postmarket surveillance for hepatotoxicity. Now we go back starting to mining various databases, including PharmaPendium as well as the FAERS database, try to find the evidence in the preclinical settings and how the, whether the sex bias effect or the phenomena already being observed in the animal studies.

Once this has been confirmed, we can conduct an in vitro toxicity assay using the primary human hepatocytes from the male and female donor to confirm these results.

After that, we are going to expand this study to a much larger number of adverse events by including more drugs.

All right, so far I said so much good words about our junior scientists in this division, and really happy and what they do. But that's really not means our senior scientists just sit in the rocking chair not doing anything. Actually, they do great.

There is another funding mechanism that actually was a center level collaboration between CDER and NCTR last year, and Dr. Huixiao Hong and Dr. Wen Zou both are senior scientists from the Bioinformatics Branch, they both received funding from CDER. Both of them actually were looking into the opioids issues using AI. Dr. Huixiao Hong more focused on the knowledgebase development called the Opioid Activity Knowledgebase and then using AI to identify what is the underlying feature driving the opioid crisis. This is going to be validated using in vitro assay which was collaborating with NCATS.

Dr. Wen Zou was trying to look into the FAERS database to identify what is the root cause in terms of the sex bias when prescribed the opioid medicines to related cardiovascular risk.

So our senior scientists also play a broad range of leadership and outreach activities. For example, in April last year, our senior scientists and actually was Dr.

Joshua Xu, and led the organization of the 18th Annual Conference for the Mid South Computational Biology and Bioinformatics Society, also called the MCBIOS2022. In May 2022, Dr. Huixiao Hong the branch chief of the Bioinformatics Branch, and he co-organized the workshop on the Cheminformatics Resources of U.S. Governmental Organizations, which was held in the White Oak of the FDA.

In September, we have the -- we also co-organized 5th Annual Conference of the MAQC Society, which also held in the White Oak, and in September 2022, the same month, our statistics branch was co-organized American Statistics Association Biopharmaceutical Section Regulatory Industry Statistical Workshop, and Dr. Joshua Xu also invited to present the R2R program at the inaugural FDA Digital Transformation Symposium.

I'll just give you a quick update on another really important project which is in collaboration with the PrecisionFDA. We call it PrecisionFDA Indel Calling Challenge. I'll just describe this challenge, in the last year, this is mainly focused on the Oncopanel. As you may know, Oncopanel has been widely used in clinical applications. Actually some have already received approval from the FDA. In order to get accurate diagnosis or prognosis from the Oncopanel, indel calling become really

important. However, there is a broad range of indel calling pipelines available.

So in this challenge, we are trying to get understanding on how to assess these indel calling performance and what is the key factors was affecting this performance, and this is just a first challenge. We will have the second challenges coming next year, and in the first phase of this challenge, we have 21 participants. They submitted like 120 applications, and we only -- this challenge only stayed on the calendar for a little over two and a half months, and we received 120 applications.

The top winner was invited to the NCTR sponsored meeting to give a presentation to summarize their results. Right now we are preparing a manuscript to summarize this challenge.

This is a summary slide. It's my last slide. I just want to convince you and I think, I hope, I managed to convince you that the division is really highly collaborative, and we are supporting our sister centers, but also we collaborate with NCTR division as well. Between 60 to 70 percent of the DBB research projects also involved the divisions from NCTR.

The division has a broad range of skillsets in the area of bioinformatics, statistics, data science, cheminformatics, and database development. More

specifically, we have emphasized more and more on the AI and machine learning, which is going to guide us in the next few years, particularly in the AI4Tox program, and we are continually developing the knowledgebase. This is sort of the longstanding tradition in this division, and we are starting the endocrine disruptor knowledgebase back all the way to 1996. So now the most recent knowledgebase we are developing is called OAK, Opioid Activity Knowledgebase.

Real-world data analysis, this is the new direction and the mainly taking place in the Biostatistics Branch, and we are emphasizing more on the electronic health records as well as the social media data.

The division is also working on diverse areas important to the FDA, and of course we are very closely working with CDER on the drug review process. We have been working on the precision medicines for many, many years now, starting the 2003 and start the MAQC/SEQC consortium efforts, and now we are transferred to the PrecisionFDA challenge, and we also have a lot of expertise in the area of genomics and toxicogenomics, and we have been doing the drug safety also for many years. In the past, we mainly focused on liver toxicity and to move forward, we're going to do a little bit more work on the kidney toxicity as well as the cardiotoxicity, and we also are starting to expand

our research area to COVID-19, opioid crisis, as well as the CBD.

I think that's it. Thank you very, very much, and I would be happy to answer any questions you may have.

DR. GANEY: Weida, thank you for a really nice presentation. I'm going to start because I have a couple of quick questions and then a comment. My first question is what fraction -- so you mentioned that you're highly collaborative and that's clear from what you presented. What fraction of your projects are initiated by your division versus you being invited or asked by other divisions or centers to help?

DR. TONG: Good question. I need to go to look at it.

DR. GANEY: Give me an estimate. Is it like 10 percent or 50 percent -- I'm just curious. I'm just trying to get a feel for it.

DR. TONG: I think it's probably more than -- first of all, our division initiate a project and has 60 to 70 percent of them as have a co-PI from the other divisions.

DR. GANEY: My other question is more of a scientific question. You mentioned that you were going to be using primary human hepatocytes from men and women to do some studies to look at drug sensitivity. Those

hepatocytes are going to be from patients who have been compromised, right? I mean, you don't get hepatocytes from healthy patients. So are you -- how are you figuring that into your results?

DR. TONG: Very good question. First of all, we really do not have a control what type of cryopreserved human primary hepatocytes we will have, and we are working with a contractor I think at the in vitro -- before we called it in vitro. Albert Lee. You probably know him. So my understanding is these cryopreserved human primary hepatocytes are not all from diseased patients. Sometimes people are just hit by the car or something, and they have that as well. So I really don't know. We did work with them some years ago, and I see the mixture of the cryopreserved hepatocytes.

DR. GANEY: Okay. I'll point out that even if they were in a motorcycle accident, those livers are probably damaged or at least inflamed in some way. Just something to think about.

And then finally my comment is you have an impressive number -- very good of you to highlight the younger scientists and the impressive number of awards that they've won. But it does go back to the comments made earlier by Dr. Lanza and Dr. Walker about they're clearly good, talented people and somebody else is going to be

looking at them and snatch them up. So it just makes it even more important that you try to find a way to keep them there.

DR. TONG: Thank you very much for the comment. Some of the young scientists I mentioned here is they graduated from the University of Arkansas Little Rock. During their graduate time, we're already starting to supervise them as mentor them, and all the way they graduated and come to the NCTR as a postdoc and then we convert them to filling in the vacancy. This is the only trick left for us to do right now.

DR. GANEY: That's good. Alex, did you have a comment?

DR. TROPSHA: I must.

(Laughter.)

But quickly, we've tortured you enough this morning. I think you've been exposed more than others today. So a couple of quick comments, Weida.

One, I noticed when Mike Eppihimer was doing his presentation that the collaboration with CDRH was sort of in the suggestive mold, was a list of projects that his center could collaborate with NCTR on. So I'm wondering if there are some ongoing plans to collaborate with them and especially which I think would be particularly good for you, Tim, in the area of medical device toxicity, because I

know just you have a database of leachables, extractable and leachables, and that come from medical devices. So I think it's a very straightforward area of interaction. That's my first quick comment and question, whether this is in your plans.

DR. TONG: Thank you very much for the suggestions, and definitely CDRH has a lot of the expertise and the resources, and also relevance to the work we do. They are doing a lot of the AI and machine learning. They released the white paper to guide the industry on how to manage and monitor the AI device with the AI embedded in there. So there's no question about it, and we need to engage with CDRH and should more closely.

Currently, we do have one project with CDRH I did not mention, and actually it is a Chief Scientist Challenge Grant at CDRH as the PI, and we as a co-PI to mainly help out the data analysis. I think we have a couple years ago, we have another project with CDRH as funded by Office of Women's Health. But with that said, and I think in sort of in much more like institutional level, I should engage with CDRH much more closely. Thank you very much.

DR. TROPSHA: And specifically, E&L compounds? That's the closest to cheminformatics, and that would be the extremely straightforward application of the tools that

you're developing and familiar with. So I just think that it's very, very low-hanging fruit and may be very useful.

DR. EPPIHIMER: We currently have a project that we're vetting with stakeholders around the use of AI learning and machine learning with regards to the chemical space. So if there's interest, we need to stakeholder it yet with our customers and our stakeholders to kind of get some feedback on it. It came up in some talks, but we need a broader -- we need to get some broader feedback on the utility of it.

DR. TROPSHA: Sure, I was just mentioning this because Weida's one of the major expertise is in cheminformatics and when it comes to chemicals leaching from medical devices, that's the immediate connection of expertise. Just suggest look into this.

DR. TONG: Just to quickly jump in, sorry to interrupt you, and actually Dr. Huixiao Hong does have a project with CDRH looking at bleach and look at the endocrine disruptors for the devices, yes.

DR. TROPSHA: So, the second is kind of related. You track how your publications are used by citations. Wondering if you track how databases that you produce are used and NIH is pushing everyone with a new policy for data sharing and management, and that databases are recognized increasingly as standalone objects with their own DOIs. So

how you track the use of databases, and a related question how you collaborate with others who might be using your data, outside -- at least publication wise.

DR. TONG: Oh, excellent suggestions. No, we do not really do diligently on that part, and we are sort of more like you build it, they will come, field of the dreams sort of thing. No. Yeah, I totally hear you. This is a fantastic suggestion.

DR. TROPSHA: Okay, if not, I highly suggest that you publish them in database issues and track them, because today the whole policy from NIH is reuse of the data and certainly databases should be exposed to the public, so should be reused by others.

DR. TONG: Only one database we have some sort of sense how many people use it, it's the liver toxicity knowledgebase, which is a benchmark dataset, and because the reason we know because that particular paper was cited very highly by the community. So we know people use that dataset.

DR. GANEY: Are there any other questions for Dr. Tong? Okay, thank you very much.

We will now have our last presentation of the day, the Division of Genetic and Molecular Toxicology, by Dr. Heflich.

Agenda Item: Division of Genetic and Molecular Toxicology

DR. HEFLICH: I am Bob Heflich, director of DGMT, and this will be the last presentation of the day, as usual. We're the last in line. I think I have figured this out. It has to do with alphabetical order. So it's not a knock on our value to FDA or NCTR. At least that's the way I'm interpreting it.

Just to mention that our deputy director is Manju Manjanatha, listed on the slide. He's presently in India for three weeks, and so he's got a good excuse for not being here.

Here is our disclaimer slide. What I have to say as far as my interpretations and conclusions are my own and not necessarily those of the FDA.

Here's our staff. We're one of the smaller divisions, if not the smallest research division. Currently we have 33 members, and it includes six postdocs and total staff of 33, as I said.

Just to go into this a little more deeply, three government FTEs left DGMT in the last year. One left for a job in industry, much better salary. One retired, and the staff fellow transferred to another NCTR division. So we've managed to start backfilling one of those positions. One of the postdocs we have left due to visa issues, which

is not uncommon, and we have acquired one new ORISE postdoc. So that's kind of a wash there.

This slide lists some of the division's collaborators within NCTR and FDA and elsewhere in the public sector, and also outside of government, including universities, nonprofits, and a few commercial organizations. The majority are not new to this year but represent long-term relationships for both conducting research projects and for developing standards and guidance documents.

Here is a list of instances where DGMT members have taken leadership positions in organizations that have had global impact. We have had leadership in several consensus building organizations like HESI, Health, and Environmental Science Institute. You're probably familiar with that. IWGT, which you might not be familiar with, it's the International Workshop on Genotoxicity Testing. Very important to the gene-tox area.

OECD of course, last year we finalized the test guideline that was for an assay that was developed at NCTR that literally has been about 15 years in the making. We have leadership in several scientific societies, like the SOT and the EMGS, as examples, and scientific publications. Barbara Parsons is currently the coeditor of the Reviews section of Mutation Research.

So here is DGMT's mission to improve public health by providing FDA with expertise, tools, and approaches necessary for the comprehensive assessment of genetic risk. Our goals are listed here. They've been the same goals for the 10 years I've been division director. Respond to agency needs for expertise and chemical-specific data; maintain DGMT's tradition of leadership in regulatory assay development and validation; and develop advanced in vitro toxicological models that incorporate genotoxicity endpoints. I've listed some examples of recent activities in these three areas.

Here are some strategies. First and foremost, engage FDA product centers and also the NTP and other national and international organizations to set research priorities. Develop better biological models for assessing human risk. Develop more comprehensive and flexible approaches for monitoring genetic variation, and finally, participate in and lead occasionally global efforts to advance genetic safety assessments by developing consensus on methods and their applications, and I've listed again several examples of each of those.

So, we've been asked to present metrics, performance metrics, expressed in these terms I've listed here. I listed several categories: publications, projects, funding, examples of leadership and regulatory impact.

You've heard about that from the other divisions that preceded me.

Here are some numbers to go along that address the metrics. I would just like to spend a little time with this last bullet, giving examples of how we participate in FDA regulatory decisions. Something that we are often asked about to establish our impact.

Several of us, seven are listed here, are members of the CDER gene-tox committee, which is a really important committee not only to CDER but also product centers throughout FDA, where we were often asked to weigh in on problems reviewers are having with submissions.

The questions often deal with assays. We have had a role in developing and establishing how they are used. So we are often in a unique position to give advice. Some of the reviewers clearly don't have very much experience with these assays. We also have participated in training sessions for reviewers. Last time with CDER was less than two years ago.

And we have participated in writing various FDA guidances this last year working on a guideline for industry and reviewers dealing with first-in-human studies on genotoxic drugs. Only this week we've got a map which is a little summary document for reviewers on policy

associated with this that's been distributed for comments. So we're working on that for CDER reviewers.

Also, we've participated a lot in guidances related to controlling nitrosamine impurities in drugs. As I will describe in a minute, we have done quite a bit of lab work to determine how best to test nitrosamine impurities for mutagenicity. That information is already being used in reviews and presented at outward-facing meetings as FDA views on the subject. The plan is that we'll eventually publish recommendations and perhaps formal guidances on the subject.

So I'd like to spend most of my time describing three current projects that illustrate some of the different types of work conducted in the division. I picked three topics that are different from each other, and somewhat different from what I've spoken on before. First of all, responding to FDA product centers for genetic toxicology data, and I'm going to use our nitrosamine drug impurity projects for that. Developing new methods for safety evaluation. I'm going to talk a little bit about adopting genetic toxicology endpoints to in vitro organotypic tissue models. I heard about NAMs and their importance to FDA.

And thirdly, updating OECD genetic toxicology test guidelines, which is an area of international

outreach, which doesn't yet involve another product center, but I think it might be of interest to people. Certainly of importance to FDA.

The first project is something that we were asked to get involved in about two years ago. We were asked to specifically by Aisar Atrakchi and Tim McGovern, from Office of New Drugs with CDER, and as you can see on this list of collaborators from CDER and NCTR, it's kind of involved a lot of people. So the objectives are to develop optimized methods to evaluate the mutagenicity of N-nitrosamine drug impurities, and N-nitrosamine drug substance related impurities, and I'll explain what that means in a minute, and the Ames test which is objective 1. And to develop follow-up in vitro mammalian cell assays, which is a second objective of this study.

This describes some of the background to this study in terms of the work we are doing with Ames testing. Ames testing is a very important to CDER. CDER uses the Ames bacteria mutagenicity assay to classify drug impurities and degradation products for their risk of causing cancer. Mutagens are suspect carcinogens and controlled at low levels.

Nitrosamine drug impurities are particularly troubling, since many are known mutagens and carcinogens, and in fact are listed as a cohort of concern in the

applicable ICH guidance, but conducting the Ames test for nitrosamine impurities is a problem, because many common methods used for the Ames test can affect nitrosamine mutagenic responses and in some cases producing negative results with otherwise powerful mutagenic nitrosamines, and while Weida was giving his talk about deep Ames, I was sort of wondering what kinds of drug impurities he was looking at.

Another issue is that very little is known about how these problems with the Ames test relate to nitrosamine drug substance related impurities, which are often called NDSRIs.

These are a recently recognized class of nitrosamine impurities formed from the drug substance itself. This has been known for maybe 30 years that drugs can form nitrosamines themselves, but it's sort of been not recognized very much in regulatory decisions. NDSRIs generally have more complex structures than in nitrosamines historically studied. It's now thought that 20 to 30 percent of all drugs in commerce can form nitrosamines by themselves. Thus there is a need for a version of the Ames test optimized for detecting nitrosamines that will increase FDA's confidence in the test findings.

The Ames test is shown in this cartoon. It's been around for more than 50 years. It might have been

called a NAM 50 years ago, actually. Although it is deceptively simple to conduct, it's extremely effective, genetically brilliant, and a vitally important assay for FDA. As many of you probably know, it involves combining indicator strains of bacteria that detect different types of mutations with a mammalian metabolic system, usually rodent liver homogenate. In our case, conducting a short incubation after everything is combined, then plating the mixture out under selective conditions, incubate for two days, and then count the resulting colonies.

Mutagens increase the number of mutant colonies relative to background colonies on control plates, and you can see on the right here the top test plate is example of a mutagenic response in the bottom. It's a control plate showing just background mutation frequencies.

So over the years that it has been used, which are quite a number, a number of protocol alternatives have been found to affect the mutagenicity of nitrosamines in the assay. I've listed several of them here. The question was what should we recommend and what should we look for in Ames test data when people submit data to FDA?

What we have done is to design a test that evaluates the most promising of these alternatives and perform testing on a series of nitrosamine impurities in NDSRIs of different classes. I've listed some of the

conditions we were evaluating in the indented points. To do these tests requires rather large assays, over 1,000 plates per chemical, involving multiple support scientists as it turns out, that CDER has been nice enough to hire for us.

The idea is to test what has turned out to be 27 compounds and to see if we could determine what is optimum for detecting their mutagenicity.

So here is some data for 13 NDSRIs we've looked at. Seven of the 13 were mutagenic using one or more assay conditions. So I have sealed the identity of the NDSRIs, because some of them are under regulatory consideration, which requires very elaborate clearance for me to talk about. But I think you can see some trends here in this data as far as the most sensitive test strains and the types of exogenous metabolic activation that seems to work best. These are the kind of data we need to advise sponsors about how to best do their tests and reviewers about what to look for when they are presented with study reports.

As part of this project, we're also exploring follow-up studies using in vitro mammalian cell systems. The reason for what we are doing is explained here. CDER held a workshop on nitrosamine drug impurities in 2021 where a bunch of experts got together and gave their

opinions about what CDER should do as far as dealing with this problem. One of the things they suggested is a need for mammalian cell follow-up assays that are geared to detect nitrosamine mutagenicity, specifically human cell assays with human metabolic capability to confirm and further study Ames nitrosamine impurity findings.

We have a couple of systems in DGMT that we employed here, and one of which was I think mentioned previously by Fred Beland, there's a series of human lymphoblastoid TK6 cells have been developed at NCTR that are transduced with different human CYPs. There are actually 14 lines, each with a different CYP transfected into it, plus the parent non-transduced line, which doesn't express any kind of metabolic activity.

So that is a system we have used. Secondly, human HepaRG cells are something we're using that express human metabolic activations, and I'll give you a little more information about these in a later slide. Very fascinating cell line.

This slide shows the rationale for the studies and the general outline of the approach. So these mammalian cell studies specifically, we're investigating if Ames positives -- of course, Ames uses a bacterial target with a rodent metabolic activation system -- are also positive in human cells with human metabolic activation

pathways. Secondly, to investigate if Ames negatives are also negative in human cells with human activation pathways, and mammalian cells in particular are useful for investigating the mutagenicity of nitrosamines inappropriate for bacterial testing, and one obvious example is antibiotics that just kill the bacteria.

These cells are used -- we are proposing that these cells be used for this purpose. So because of the number of things that could be tested, you know, that one TK6 system has essentially 15 different cell lines associated with it, and the difficulty of doing mutation assays in mammalian cells, we have staged these studies by first screening for genotoxicity using high throughput assays and then concentrating on the most promising conditions for doing mutation assays. I'm going to talk about some TK data first here.

So an example of this is shown here with one of the NDSRIs that was named positive, NDSRI 8, that was screened in several CYP-expressing TK6 cells using a flow cytometric assay for measuring micronuclei, which is essentially chromosome breakage. And yes, we found that human CYP2C19 was metabolized NDSRI to produce micronuclei, and you can see that in the circle here, the increasing bars showing increasing micronuclei, and look at the very

small doses involved in this. This chemical is really potent.

And we have retested this using this cell line to investigate mutation at the HPRT and TK locus, which you can do in TK6 cells, and, yes, it is also a gene mutagen as being a clastogen. So NDSRI is something we should pay attention to. This data is presently in review and submitted to a journal. And it even discloses the name of the NDSRI. So you could find out what it is.

A second topic I'd like to bring to your attention is our continuing efforts to adopt genotoxicity endpoints to in vitro organotypic cell cultures. Sometimes they are referred to as NAMs. The hope is that these types of advanced cultures will enable risk characterization in a more sophisticated manner than is possible with traditional 2D cell lines, and perhaps it can be the basis of quantitative in vitro to in vivo extrapolation, perhaps reducing the need for animal usage.

We have been using these in vitro models in several projects in the division going back 10 years in the case of the airway model I will show you in a minute, but mainly measuring biochemical and physiological endpoints. Measuring gene-tox endpoints in these cultures has been a challenge because many of these models consist of fully differentiated cells or mixtures of cell types, some

dividing and some not. This is all necessary for organotypic nature of the models of course, but presents challenges for doing gene-tox measurements, using traditional approaches, which rely on cell division and sometimes single cell cloning.

Anyway, we have been concentrating on two systems, one the ALI airway culture we have been using for collaborative projects with CTP, NTP, CDRH on the toxicity of inhaled substances. Dr. Van Bemmel referred to this model in her CTP talk, and also referred to the fact that we were going to compare the genotoxicity of different products using this model. So we better get on the stick about determining, developing gene-tox endpoints.

So far, we have been successful in developing a method for doing DNA damage using a Comet assay type system called the Comet Chip, and gene mutation using an error corrected next generation sequencing method, and I talked about this last year. So I'm not going to tell you how that works. But if you're interested, it's in this paper that I have cited down here.

What we are stuck on is developing a micronucleus assay for this particular cell model, and we have some ideas, some of which we've tried and not been successful, but I have a real hot idea that we really want to give a try in the next couple of weeks.

So here is the HepaRG cell cultures, and this has mainly been used in CDER projects so far, and again, we'd like to do DNA damage in these cultures. We'd like to do gene mutation, and we'd like to do the micronucleus assay. Now in this case, we've developed a micronucleus assay for these cultures, and Comet you can do on anything, so that's not a big challenge. But gene mutation has been a problem. We just haven't started -- a lot of these things are unique. I mean, they've never been done before. So this is sort of breaking new ground.

So one thing about HepaRG cells is they can be grown several ways, and on the right of this slide is a 2D culture where they're sort of spread out. So typical hepatocyte shape you might be able to make out. But they will also form spheroids, and you can see on the upper right panel with all the little circles in it, these are different concentrations of cells that have been asked to form spheroids in a low binding 96-well dish, and you can see how they aggregate together.

The interesting thing is about this is they really act a lot more like in vivo hepatocytes and spheroids than they do spread out in the conventional 2D culture methods. So this is all described in this paper on the bottom here. It gives you sort of an insight about the micronucleus and the DNA damage parts of this.

So these cells, the HepaRG cells, were originally isolated from hepatocarcinoma of a female patient with chronic hepatitis C virus infection. They are actually liver progenitors that can be differentiated into cultures that retain many characteristics for primary human hepatocytes, including morphology and expression of phase I and phase II metabolic enzymes.

The differentiated cells can be maintained as attached 2D cultures or unattached spheroid cultures, as I showed you, and these spheroid cultures have increased metabolic activity. The interesting thing about this is that differentiated cultures can be stimulated to divide, express micronuclei, and theoretically fix mutations by adding growth factors to the media.

So Jieun Seo and Xiaoqing Guo recently conducted an experiment where they formed cultures that differentiated HepaRG cells from both these 2D and 3D cultures, treated with NDMA dimethyl nitrosamine, and then stimulated them to divide with epithelial growth factor. Along the way, they were able to measure DNA damage with a Comet assay, clastogenicity and aneugenicity with a micronucleus assay, and after some growth in culture, mutation using two error corrected next generation sequencing approaches, duplex sequencing using an Illumina

platform, and hi-fi sequencing using a PacBio Sequel II instrument.

So I'll show you the PacBio result. Mutations were found. We may have overdone it a little as far as the dose is concerned, and you can see the mutation sort of flattens out at a mid-concentration, but definitely a positive increase. And the mutations that we found, NGS actually sequenced, determines the mutations by the sequence. So you get a sequence readout. What you would expect from NDMA in vivo. So this is very encouraging, and encouraging the collaborators on this to put this together and publish it as soon as possible.

This obviously requires a little more work, however, to optimize the conditions, but we were very encouraged that mutation can be measured in this model and that somewhat familiar gene-tox endpoints can be measured in NAMs with a little adaptation of approaches.

Okay, here's my third project. It's going to be something a little different but it's something I've been dealing with personally for the last few weeks. It's an illustration of how some of our division members become involved with important work of developing guidances, standards for use by the reviewers, and making regulatory decisions. This problem became obvious to me during the development of the Pig-a OECD test guideline and of course

that's, as I said, that took 15 years, so I had a lot of time to think about it.

Several of us were thinking about this project have come together, a consortium of projects from myself, a person from Litron Laboratories, which is a CRO, Health Canada, which is the regulatory agency in Canada, and St. George's Medical School in London, are proposing to revisit how responses in genetic toxicology, OECD test guidelines are evaluated, starting with in vivo test guidelines that we have taken a very, very detailed look at their performance. Most current OECD gene-tox test guidelines and other toxicants test guidelines also recommend evaluating whether response is positive or negative by applying equal weight to three considerations. One, whether the chemical produces a statistically significant increase compared to the concurrent negative, whether the response is concentration or dose related, and whether the response exceeds the distribution of the historical negative-control database.

So criteria A and B establish the statistical relevance of the response. Criteria C was included in the OECD test guidelines about 10 years ago to test biological relevance, because that was something that people felt was critical to evaluating mutagenesis in particular. Too many positives was the problem, according to some people.

Most test guidelines provide some guidance on establishing historical databases, but almost no guidance on describing their distribution and no guidance of how to demonstrate that the distribution describes the biological variability of the assay, which is what it's supposed to do. If criteria C does not measure true biological variability but is more a reflection of poorly conducted studies, we are concerned that otherwise positive responses could be evaluated as equivocal, resulting in misclassification of test substances and/or retesting with resulting waste of animal resources.

So we propose that there are several useful ways of evaluating the quality of historical control databases that could -- that should be employed before using the data for biological relevant criteria C assessment, and I've listed some of them here. The last one, variance component estimates, including the research of maximum likelihood analysis, I'm going to show you a little data in just a minute using that.

So here are some data. Here's an historical database of liver Comet data from a CRO plotted in a C-chart, which we are recommending showing in reports to FDA submissions. The x-axis is individual animal results, grouped into studies conducted as a function of time. So here is a bunch of studies conducted over a year or so,

let's say. You can see variability in the results, but no obvious differences between studies or trends over time. What you would expect if the data reflected biological variability of the endpoint.

On the bottom here, this table is a variance component analysis that reflects this conclusion. Most of the variability is associated with the animal and not the study. What you would expect if these data reflect true biological variability. So all this analysis in this long story is in a paper we've submitted to EMM that's currently in review.

Now take a look at this liver Comet data. You can see there's a major difference, and it comes from another CRO. You wonder what the time factor is here, whether or not their paycheck came on a particular day to influence what was going on with these data. It's fairly obvious that there is something wrong here, and any limits constructed from these data are not a reflection of biological variability, but a reflection of technical troubles in the lab, and you can see on the bottom here that this conclusion is supported by the variance component analysis shown at the bottom. So you can see in this case most of the variability is associated with study ID and not the animal. So that's a problem, at least in our minds.

So here is our plan. We have contacted a bunch of national coordinators, the OECD runs through sort of a complicated hierarchy of people, and from the 34 or 38, I forget, OECD countries we've contacted people from U.S., Canada, and the UK, because that's where we are, and they're going to introduce a proposal at the spring OECD meeting when the workgroup of national coordinators get together to set their agenda and sort of get their feedback and find out whether they are on board with our pursuing this as a wholesale, more or less wholesale revision of OECD test guidelines.

So if they're on board with us, and we have very positive feedback from the OECD secretariat. I was sort of shocked by the enthusiasm by which they greeted our proposal, because it's going to be a lot of work.

We plan on submitting a formal proposal this fall to be considered at the next 2024 WNT meeting. They have a process we have to go through. We may form a group with HESI, an expert group, to sort of keep the flame going and sort of make some progress on some of the loose ends that we have discovered about the situation. After WNT approval, there will be an OECD expert group that will be formed and they will sort of take over. Then the reviews, and hopefully we can get this all wrapped up in two years.

I was asked to also list some challenges we have in DGMT. Tucker mentioned the two I would bring up if he didn't bring up, I would certainly bring them up, and one is our budget problems and the timing at which we get money during the fiscal year and the fact that it disappears at a particular point if you don't spend it, a short period of time. The other is frankly something that Fred mentioned also, attracting competent people, and keeping competent people at NCTR, to conduct the studies we have. We have money to support scientists and we don't have scientists to spend that money on in a couple of instances. So that's kind of sad.

Here are some other things that sort of bug me. Dealing with international suppliers, you know, dealing with the federal government is tons of paperwork and it's even worse when it involves different countries and we have people who synthesize some of our nitrosamines that are invariably not in the United States. They're in Canada or India, someplace like that, that we have to deal with and import all this stuff through customs.

Maintenance of some of our equipment has been a problem. We have a number of smoking robots and a vaping robot, and a microphysiological system, that are made in Germany, and getting repairs on this has been a major problem, especially since our wifi, guest wifi, doesn't

work very well, at least that I can tell, in the building I'm in. So that's been a major problem getting people to fix relatively small problems and sometimes we are just forced to ship everything back to the home country and go through that importing and exporting business to get it fixed.

And this happened with CTP, a project just this year, that we had to ship some exposure modules for a vaping aerosols, exposing cells to vaping, product aerosols, back to Germany for them to repair them. It took maybe three months to do that.

Another problem we have is NGS capacity. FDA doesn't seem to have a core facility for doing this with high throughput next generation sequencing instruments, which is becoming more of a problem for us, because we're essentially forced to ship money out of FDA to contractors to do sequencing that we could very well do in-house if we had the equipment or at least decent equipment, I should say, rather than the midrange of NGS that we have now. This is becoming more and more of a problem as genetic toxicology goes further along the path to evaluate mutation using sequencing rather than phenotypic identification of mutants.

We submitted a contract to obtain an NGS that will increase our throughput tenfold, if anybody knows a

funding -- has a spare $800,000 that they want to contribute to us to be able to buy such a instrument, we'd be happy to set up a collaborative laboratory with such an instrument to keep it going.

Even when we have contractors to do NGS, many of them have foreign ties. Most of them have some kind of a Chinese connection, and that's a problem for FDA.

DR. MENDRICK: Bob, this is Donna. Please end soon because you're running late.

DR. HEFLICH: Okay, so they fall on and off our list. For me at least, maintaining close collaborations with FDA product centers has been a problem with many of the friends I have have been retired, a lot of people we work with switch centers and we have to make new connections. So that makes life a little more difficult.

I think I'll end there. That's it. Thank you for your attention. Any questions?

DR. GANEY: Thank you, Bob. Are there questions for Bob? The other advantage of being last is that everybody is so tired that they don't have -- they can't think of a question to ask.

DR. HEFLICH: I usually have enough energy or enough adrenaline to get through 30 minutes, but I'll probably crash in about five seconds if nobody asks me a question.

DR. GANEY: Thank you, everyone, for your attention for being here today. We will start tomorrow at 9 a.m. Eastern or 8 a.m. Central, and the crack of dawn for you, Mary Ellen and also John Michael, and we will hear from the remaining three divisions tomorrow and then we'll wrap up with some comments for the director and the division directors. So thank you.

DR. MENDRICK: I just want to note that there is a different sign-in information for the public tomorrow. So please go to the NCTR Science Board website and see the different sign-in for the public. This is for public access tomorrow. There is a unique code for each day for public access.

DR. GANEY: Will we all receive another email for tomorrow's code?

DR. MENDRICK: Probably.

DR. GANEY: Okay. Thank you, everyone, for a really good meeting, informative meeting. I'll see you tomorrow.

(Whereupon, the meeting was adjourned at 6:15 p.m.)