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National Center for Toxicological Research

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P R O C E E D I N G S

DR. SLIKKER: Good morning, everyone. It is always a great pleasure to be able to recognize individuals that have been in service to FDA and to NCTR, and today we have really a special opportunity to celebrate our leader of this group, Pam, and her commitment to NCTR and the Advisory Board from October 2014 to June 2019. We are very pleased with your service. Pam, why don't you come up. I would like to give you this award in recognition of your distinguished service to the people of the United States of American. Can't get much better than that.

(Laughter, applause)

DR. MENDRICK: This is Donna. The other announcement is that Mickey has volunteered to take over as Chair after Pam's leaving.

(Applause)

DR. LEIN: Thank you very much. It has actually been a great pleasure to serve on this Scientific Advisory Board. I am always impressed by the work that is being done at NCTR and the interactions between NCTR and the other centers of the FDA. As a person in the academic world, it is really encouraging to me to see the work you are doing, and as a citizen of the United States I do appreciate the work that you are doing, so thank you very much. It has

been a privilege to serve for you.

So, we need to move on. This morning we are going to hear from the centers and hear their perspectives and hear how they are working with NCTR. First is going to be Denise Hinton.

Agenda Item: Statement from the Chief Scientist

REAR ADM. HINTON: I just want to say good morning to everyone, and I am truly pleased to be here to kick off the second day of NCTR's annual Science Advisory Board meeting and to welcome our lawnmower again. It doesn't bother me. The grounds are beautiful.

(Laughter)

I am always impressed by the scope of research that NCTR does to support FDA's work and also by its leadership. NCTR's work is critical to the development and evaluation of emerging toxicological methods and other new technologies that play such a large role in FDA's regulatory decision-making and in protecting and promoting our public health.

On that note, I have to step out to take care of the lawnmower dude, but I want to congratulate Dr. Bill Slikker who just received the 2019 Mildred S. Christian Career Achievement Award from the Academy of Toxicological Scientists for his extraordinary scientific achievements

through publications and professional and leadership activities, all of which have enhanced the practice of toxicology.

Through NCTR alone, within 2018 they have had over 170 research publications, done over 135 presentations, five patents, 159 active research projects, many of which were leveraged by federal agencies through interagency agreements and some through other non-governmental organizations. Congratulations, Bill, we are very proud of you.

(Applause)

I would also like to acknowledge Dr. Anil Patri for leading interagency efforts in nanotechnology. We spoke to this a bit yesterday and I just want to continue to thank him for his significant contributions to the U.S.-India science and technology cooperation which contributed to the development of the India Nanopharmaceutical Guidance Document. It would not have happened without his efforts, so we continue to welcome his engagement in that space and to further advance the field.

NCTR holds a unique and foundational position at FDA because it is the only center that supports all FDA offices and product centers with the essential toxicological research that they need to conduct their

scientific activities. It underscores the criticality of toxicological research for everything FDA does to advance regulatory science.

In listening yesterday to NCTR's achievements over the past year, I think you have to agree with me that NCTR has been making remarkable contributions both within the agency and with our domestic and international stakeholders. I will say right now that my office, the Office of the Chief Scientist, has been and will continue to be fully committed to raising awareness of NCTR's scientific research and its impact on our regulatory decision-making and to public health and, also, supporting NCTR in its work to protect public health and advance innovative tools and approaches that are critical to FDA's predictive capability and our ability to predict risk and efficacy.

NCTR's research has been a regular feature of the now monthly FDA Grand Rounds webcast that OCS launched in 2016, and the goal of the Grand Rounds has been to raise the visibility of FDA's research and describe how FDA is applying that research to its regulatory activities. Recent NCTR Grand Rounds presentations have included collaborative research into BPA and ongoing safety assessments that have earned national attention from the National Public Radio

and the like.

Another focus has been NCTR research into Alzheimer's disease in women and minority populations, as we heard from Sherry yesterday, which received funding through an Office of Minority Health intramural grant. And we can't forget the upcoming September 11th and 12th FDA Science Forum, and this is also supported by the Office of Chief Scientist. All the FDA centers and offices have been engaged in the Forum's organization and in shaping its key topic areas including tools to predict toxicity and the efficacy of FDA-regulated products in humans and in animals.

NCTR has had a leading role or has participated in numerous FDA working groups including in toxicology, emerging scientists and artificial intelligence, just to name a few working groups whose efforts are coordinated and supported by the agency as a whole and a lot within the Office of the Chief Scientist.

As you know, in late 2017 the Toxicology Working Group developed and issued FDA's Predictive Toxicology Roadmap. And in September of last year, the Tox Working Group turned to our academic, industry and federal stakeholders in our first public meeting on the roadmap to solicit input on how we could work with them to spur the

development and evaluation of new technologies and incorporate this input into regulatory review.

Members of the Toxicology Working Group have continued to participate and lead interagency groups such as Tox21 and the Interagency Coordinating Committee on the Validation of Alternative Methods. This is to further our collaboration in advancing the goals of the roadmap.

The group's efforts are also involved in the formation of an *in vitro* systems working group, of which NCTR has a leadership role, and, working through the Emerging Sciences Working Group, NCTR has been spearheading efforts to scan the horizon for future trends in science and technology that may affect products in our regulatory portfolio five to 10 years down the road. As part of this proactive posture, the group has identified artificial intelligence as a significant tool and formed a new cross-agency group dedicated to its study and application in FDA's scientific activities.

OCS staff are excited to be involved in this project and we are proud to have NCTR kind of leading these efforts. What I can say is, like on a lot of these efforts and within the working groups, there are stand-outs. I think they are cross-agency. We have representatives from each of the centers that are represented on a number of

these working groups, and many of them are led by Donna Mendrick herself, so we appreciate her efforts and leadership in a lot of these roles. I say sometimes that she is spread very thin, but she is not. She can handle it.

Finally, I would like to recognize the important role NCTR plays in promoting global standardization of regulatory science in its work with our international partners. Under Bill's leadership, NCTR established the Global Summit for Regulatory Science in 2011 and he spoke to this yesterday. This brings together leadership from nine countries in the European Union each year to focus on regulatory science research. These partnerships like the Global Coalition for Regulatory Science Research are focused on modernizing safety assessment through global exchange, training and collaborative research with toxicologists and other scientists worldwide.

Just another reminder that this year's global summit is taking place in Italy from September 24th to 26th, and that is just 12 days after FDA's Science Forum, so mark your calendars. It is going to be a busy month.

Now I will turn the podium over to the centers. I really look forward to hearing more about all the work we are doing together to advance science and increase the impact of toxicology. Thank you.

(Applause)

DR. SLIKKER: Denise, I just want to thank you for your kind comments and your leadership at FDA Headquarters for the NCTR and the other centers and our role in science and research. It really is a privilege to see the communications that you have built between the various centers and between the NCTR and the rest of the agencies, so we really appreciate your support and your fine work in this area.

Agenda Item: FDA Center Perspectives

DR. LEIN: Thank you very much. I think we will start with the center perspectives. The first is Center for Biologics Evaluation and Research. Carolyn Wilson.

Agenda Item: Center for Biologics Evaluation and Research

DR. WILSON: Good morning. I am excited to have an opportunity to spend a few minutes to share with you an overview of the center, the products that we regulate and a little bit of information about our research goals, the facilities and expertise that we have at the Center for Biologics in terms of our intramural research program, and then how we are interacting with NCTR to complement each other’s needs.

Just the normal disclaimer that this was an

informal communication representing my own best judgment.

The products that we regulate are what we call the complex biologics, and it is sometimes confusing because people are most familiar with the biologics that are regulated by Center for Drugs, things like monoclonal antibodies and therapeutic proteins. But we also regulate some therapeutic proteins, a subclass that are historically derived from blood, typically clotting factors and the like, but most of those are over in Center for Drugs.

The kinds of products we regulate are very complex and challenging from the point of view of understanding how to characterize them, having appropriate models to evaluate them and so on. The first one listed here, allogenics, actually represents a class of products that HAS over 1200 different allogenic extracts used to both treat allergies as well as to diagnose. Blood and blood components obviously are things that have huge public health impacts. And blood derivatives, devices related to biologics -- and that includes things like devices used to separate blood into its components as well as other devices used to isolate cell therapies, for example.

Gene therapies, human tissues and cellular products, and, of course, some of those cell therapies are also gene therapies, vaccines, both preventive and

therapeutic, live bio-therapeutic products -- that's a class of products that includes things like fecal microbiota transplantation, things that in the CFSAN world are often called probiotics, and also things like bacteria phage therapy, novel approaches to treating bacterial disease. And then xenotransplantation products.

So, what a lot of these products share, in addition to the complexity, is that these also cannot be terminally sterilized, and so there are challenges that they are always derived from biological products, and they may also have contaminating infectious agents. So these are challenging to regulate on a variety of fronts.

Our research goals are developed by the center's Regulatory Science Council. These are actually just our very high-level, center-level goals, and I won't go into them. But each of our offices that have research also have their own more specific set of goals and research objects, but ours are really to cover the waterfront.

So, advancing the scientific basis for regulation of biologics, human tissues and blood by developing and evaluating technology reagents and standards to inform and improve chemistry manufacturing controls; developing and assessing nonclinical models and methods predictive of clinical performance with respect to toxicity and

effectiveness; improving clinical evaluation pre and post-licensure, and preparing for future regulatory and public health challenges.

In a few minutes I will be going through some examples of collaborations that we have with NCTR that are in support of the first two research goals in this list.

As I mentioned, we have our own intramural research program in the Center for Biologics. We have a variety of applied and analytical technologies. We are heavily invested in methods development in NMR and mass spectrometry, developing high resolution analytic approaches to evaluate the products we regulate. We use flow cytometry, micro-ray, high throughput sequencing (also known as next-gen sequencing) all to support the research that we are doing.

As you would imagine, with the kinds of products we regulate we have very strong expertise in microbiology, immunology, biochemistry, molecular and cell and developmental biology. And a relatively new area, tissue engineering and microphysiologic systems is an exciting area for us and one where you will see there have been some crosscutting collaborations with NCTR in this space.

Epidemiology is important for us as well as, of course, biostatistics. And bioinformatics is an area that

we have been continuing to invest in and we recognize a need to really continue to expand our abilities and expertise in this area.

Our facility at White Oak -- I should say our laboratory -- is located on the White Oak campus. We provide a variety of core facilities to support the research and a state-of-the-cart vivarium. I won't read through all of these for the sake of time, but just to make you aware.

Obviously, we don't do everything by ourselves. In addition to collaborating with NCTR we collaborate across the nation, across the globe and in a variety of sectors, and that includes other FDA centers including NCTR and other government agencies. A very large sector is associated with academic collaborations and even international as well as industry, international government agencies, nonprofit and so on.

I am going to spend the last few minutes to talk about the collaborations we have with NCTR. The first set I will talk about is in support of Goal 1, which is chemistry manufacturing and control. So this is really around product characterization. There are three major projects. I am not going to talk about all of three of them.

The first one on pathogen detection in fetal

microbiota transplantation is ongoing but has no major updates at this time, unless Carl may have mentioned some that I wasn't aware of. The second I will talk about, which is detecting target mutations and their biological effect in gene editing, and the third is relating to chimeric antigen receptor T-cells. Actually, this was awarded the Chief Scientist Challenge Grant, so this will be starting fairly soon.

The first is a very exciting area. As I am sure everyone knows, gene editing has got a lot of buzz. It is a very exciting technology with great capability and promise. But, as a regulatory agency, we are always looking at the potential risks associated with new technologies, and it is not a surprise to anybody who is paying attention that one of the major risks that we are concerned about is off-target mutations.

So, in collaboration with Javier, Dr. Yi is going to be looking at new sensitive methods to detect and provide functional evaluation of unintended mutations in human gene therapeutic products using genome editing technologies. We are doing this with NCTR because of the experience in genotoxicity and next-gen sequencing, and you heard about this yesterday as well from Bob Heflich. We are excited because the outcome of this study could have a very

important impact in helping us to address the significant regulatory challenge in evaluating the safety of this new technology.

The other area is also very important in addressing another cutting edge area that our center regulates which is chimeric antigen receptor T-cells. I am sure, again, many of you know that last year the first two gene therapies that are based on CAR-T cell technology were licensed, and this is just the start of a much broader pipeline of products.

This is a collaboration with a variety of scientists here at NCTR, and on the biologic side it is led by Nirjal Bhattarai. We find that, even though CAR-T cells are a very exciting area, there are still challenges and questions around what are the critical attributes in terms of characterizing these products. The work will be centering around developing novel *in vitro* and *in vivo* models that will be used to help identify the critical quality attributes that correlate with safety and efficacy. Again, if successful, this product has a potential impact to provide very useful insights to assist the regulatory review of these therapies.

Now moving into Goal 2, which is again abbreviated for a reminder as sort of the nonclinical area,

there are four major projects. Two of these are complete so I won’t go into any detail about those. One was looking at codon-optimized therapeutic proteins using ribosome profiling to evaluate the impact of non-synonymous mutations. That was completed and has been presented at six meetings over the past two years.

The second one that is complete also has two papers coming out of that, and that is looking at pharmacokinetics and bio-distribution of novel adjuvants in the context of vaccine use.

The two projects I will go into in a little more detail is some work on clostridium difficile, and this was mentioned by Carl yesterday, as well as some norovirus work.

This is a collaboration between Doug Wagner and Paul Carlson and is looking at host pathogen-microbiota interactions during clostridium difficile infection in fecal microbiota transplantation using a human enterocyte cell line. As Carl mentioned, there is very deep experience here in microbiology and the microbiome, and we are excited because this is a fairly challenging model to stand up. Now Dr. Wagner has developed this hybrid *in vitro* culture system using the human HD29 enterocyte cells and an anaerobic incubation system and already he has been able to

demonstrate proof-of-concept by showing cytotoxicity in the presence of c. difficile and other commensal strains and is starting to get more information about the immune response both in the context of c. difficile alone or when various commensal organisms are added. And this has a component of metagenomics analysis after co-culture.

In addition, they are doing a mouse challenge model using an antibiotic treatment to allow for c. difficile to take hold and are looking at the pro-inflammatory cytokine response. This work has the potential of providing us an improved understanding. One of the challenges with fecal microbiota transplantation is that really none of us are super-thrilled about having a product that’s based on human feces, for obvious reasons. So, being able to dissect out what are the critical commensal organisms or the consortia of organisms that are really providing this therapeutic effect against c. difficile or other therapeutic applications would be a huge breakthrough in allowing this field to develop to the next stage.

The other one under Goal 2 is on norovirus vaccine development, and probably everyone in this room has had the pleasure of a norovirus infection. If you haven’t had it, it’s the one that you constantly hear about on the cruise ships. It’s really nasty. The problem is that there

is no cell culture model, there's no animal model, and this really hampers our ability to develop a vaccine because how do you evaluate it.

Gabriel Pardo has been collaborating with Marli Azevedo, who has a large number of canine samples infected with noroviruses, and together they have actually isolated and sequenced the first 10 canine norovirus genomes and these have been deposited in the public database. Already they are identifying certain characteristics that are important to understand why they have limited zoonotic potential. Along with that observation, we are hoping that this may provide some useful opportunities for adapting to animal or cell models.

The last couple of collaborations I wanted to talk about don't group necessarily with our research goals because it's kind of the opposite side of a research collaboration. These are collaborations where there was ongoing research here at NCTR and they reached out to our scientists because of expertise that we can provide.

In the first, which I won't be talking about because this has really been on hold, is a project that was initiated at NCTR using a method developed here called S-STAR which I will not talk about, but they developed some candidate drugs for Chagas disease. Alain Debrabant in our

center is an expert in Chagas disease and has *in vitro* models that can be used to assess these drugs. That work has not progressed, as I mentioned, because it's on hold.

The second area -- again, this is one where it actually has been approved and has started, and Bob also mentioned this yesterday -- is this *in vitro* spermatogenesis model, and I will talk about that a little more. And there is another project which just got funded through the Perinatal Health Center of Excellence with the same investigator, which is around developing an *in vitro* placental barrier. I won't be talking about that in more detail, but just to mention it.

The microfluidic system is a collaboration between Drs. Nakamura and Mattes, and they are really taking advantage of Kyung Sung who is here in the Center for Biologics and her expertise in microfluidic systems. What they have realized is that as they develop these *in vitro* tests of organ cultures, they see necrosis at the center, so, what they are hoping is that the microfluidic experience can help them to develop this model into one where the oxygen deficiency can be addressed. Obviously, if this is successful this would be a very exciting opportunity to have an alternative model for assessing drug toxicity and comparing between species and within species.

To summarize, I will finish with saying that CBER is really grateful for the expertise that NCTR brings to help us develop methods and approaches to evaluate our regulated product portfolio, current portfolio of collaborations including new methods to assess cell and gene therapy products, and investigating new opportunities for models to assess treatments and vaccines against pathogens with significant morbidity and mortality. And then the inverse also happens where NCTR is leveraging our expertise to address some of their research needs.

The challenges overall in these collaborations are, first, identifying the synergistic opportunities. As was mentioned by several people yesterday, it is often best accomplished scientist-to-scientist, but, obviously, the geographic distance can present a challenge. I will just add to others' accolades for Donna as the D.C. rep who really reaches out to the Centers and does a really great job to sort of be that communication interface to help facilitate these interactions.

I think lack of funding can also sometimes be a barrier to making good progress on the research. Sometimes the Center for Biologics may not have the additive funding needed. Sometimes NCTR doesn't have the additive funding needed, but we have been fortunate in a couple of cases as

you saw today in getting these intramural research grants through the Office of the Chief Scientist which can help facilitate the research. And again, just the geographic separation can also lead to difficulty in communication.

I will stop there and am happy to answer any questions.

(Applause)

DR. LEIN: Thank you. We have three minutes. Any comments or questions from the SAB?

DR. SLIKKER: I just want to say first of all thank you very much, Carolyn. You have always presented the science in such a way that I really know you understand it and you appreciate it, and it makes everybody feel a lot better that you have a fundamental understanding of where we're going and why we are doing this work together.

The other thing is you mentioned the artificial intelligence group that Donna is heading up but it's an FDA-wide activity. It is one that you and I and many others have been fighting for over many years. Both of our centers have invested in this area but still have challenges. And some of them were mentioned in this group's description, things like making a sandbox available so we can actually test out some of these things and not be caught up in the cybersecurity issues.

And how to get both software and hardware quickly and not have that tied up in lengthy acquisition times, and opportunities to work together on these kinds of issues. These are things that you and I have been working to try to overcome for many years, and many others here in the audience.

I just appreciate this happening and that Donna and others can help lead this forward so maybe we can have a voice that we can overcome these challenges. I know you think it's important as well.

DR. WILSON: Yes. I actually didn't mention that in my talk but thank you for bringing it up. I sort of alluded to it in the bioinformatics piece. It is an important area where I think in general the agency is dabbling in various ways in all parts of the agency, but it's really time to take a more strategic and proactive approach to supporting and making sure we continue to move into the 21st Century and keep up with the rest of society's development so that we are prepared to regulate and use these technologies.

DR. LEIN: Thank you. Are there any other questions or comments? All right.

Our next presentation will be from the Center for Drug Evaluation and Research, Juan Ruiz.

Agenda Item: Center for Drug Evaluation and Research

DR. RUIZ: Good morning, everyone, and thank you to the organizers for inviting me here on behalf of CDER. I do not have a disclaimer slide but I will piggyback onto the one that Carolyn just showed which is very comprehensive.

My talk this morning is going to be in two parts. I am going to tell you a little bit about our Research Governance Council which has been implemented at CDER, now going on its second year. I will give you a little progress update on what the RGC has accomplished thus far, tell you about a five-year strategic plan that we have developed for the Council, and try to explain some of the research portfolio oversight responsibilities that we have and what are the benefits that we see from organizing such a group.

The second part is going to address the scientific review process that CEDR is providing for NCTR submissions, the regulatory science impact of the NCTR-CDER collaborations, and then we will have some time for questions and feedback.

CDER’s Research Governance Council was chartered about two years ago and was endorsed by Dr. Woodcock with a general direction of overseeing the central research

functions center-wide. We set out to develop a set of research goals, objectives and priorities; developed a system for tracking research investments as well as developed research outcome metrics so we could keep track as we make progress on those objectives.

One of the charters for the group is to provide a system so that we are able to do a periodic evaluation of the projects and portfolio of research projects within the center. Another function of the group is to review scientific interactions with non-CDER FDA centers and offices, and we want to be able to foster that collaboration further, and, finally, to provide general oversight of CDER-wide research programs and policies.

First, right off the bat what we did was to develop a set of research goals which was endorsed by CDER leadership and by Dr. Woodcock -- five general, relatively big buckets of goals. Under each goal listed here are three to four objectives within each goal, and then we have certain metrics so that we can gauge the progress we are making.

First of all, to develop and improve scientific approaches that aid in developing new drugs or evaluating their premarket safety and efficacy. The second goal is to develop and improve scientific approaches to enhance the

safety of marketed drugs; third, to improve product manufacturing, testing and surveillance to help ensure the availability of high-quality drugs; fourth, to develop and improve methods for comparing products to facilitate the development and review of generic drugs and biosimilars; and, finally, maintain the scientific readiness to address emergency public health threats, enable regulatory integration of emerging technologies, and facilitate stakeholder adoption of novel approaches to drug development.

The RGC was formed and has organized several working groups to address the different aspects to develop a framework for the organization. There was a working group that focused on developing and defining those goals and objectives and priorities, and that was finalized and endorsed in December of 2017. This was in time for our fiscal year 2019 budget data call to the offices which happened around January 2018.

A second working group out of the Office of Management focused on developing tracking mechanisms for budget and spending, so, research-related budget requests. That tracking mechanism was implemented in January 2018. Then we wanted to not just catch budget requests related to research but, on the back end, on the spend side, developed

a tracking mechanism so that we could link projects spending to research goal, objectives and priorities, and that was implemented in October 2018, and the Office of Management and Budget worked very closely with us to set that up, and a big thank you to them for that effort.

Another working group focused on developing research outcome metrics to determine how CDER will evaluate research programs against research goals and objectives, and that was implemented in October 2018, in time for initiation of the fiscal year 2019 research programs and projects.

A fourth working group, a research tracking group, was chartered with developing the databases and facilitating updates to the CDER science database, and I just want to take a moment to thank Carolyn and her team at CBER because the database platform is contained within the CBER servers, and her team has been tremendously helpful in helping us tweak the functionality of the database to address the needs of the CDER research community. So thank you, Carolyn.

We developed also a uniform project initiation process and that was implemented in the spring of 2018 and it was just in time for the research project data collection for fiscal year 2019.

A fifth working group is the communications group. That group was chartered with communicating the work of the RGC, spreading the news around the center, raising awareness within CDER of research and resources, because one of the things we found was that information was not readily available equally throughout the different offices. Also, the group is chartered with generating ideas to tell the research story that happens within CDER, and that has actually made it into the external-facing website, science and research website for CDER.

All this information is available on the intranet, the inside FDA intranet, so if people within FDA want to learn a little more detail, you are welcome to navigate through that.

Having that platform in place, then the big deal is that we want to link all these research activities to a research goal and objective and priorities. Not every project needs to be linked to a priority, but if they do, we want to capture that. Some of these activities we are already tracking, as I mentioned, budget, spending, project outcome measures. We have gone through two cycles, the FY2017 and FY2018 project updates have been done.

We have tweaked some of the outcomes based on looking at the self-reported information and whether these

outcomes are being understood by the research community. As I said, these are self-reported information so we want to make clear to the researchers what it is that we're looking for. So we did make some tweaks and adjustments and we will probably make further tweaks in the future.

As it turns out, we have not linked the ORISE spent at this point in time, although within the Office of Translational Sciences in CDER we administer the ORISE program. They have their own database or spreadsheet. We want to very soon -- and we have been in discussions with that group -- track the ORISE spend to research goals and objectives.

Also, the tech transfer activities are managed or administered for CDER out of the Office of Translational Science, and we will be also adding that information to the database. We still have not linked all the office reports, but as you can see we are linking all the research-related activities to goals and objectives.

We have developed a strategic plan, and the vision is to be the benchmark for governance of mission-driven research. We have developed four overarching areas where we want to focus. The RGC wants to optimize research activities through effective stewardship, and that is to identify best practices when evaluating projects. We want

to influence processes and policies that impact research at the center. We want to serve and we want to be the informational hub for CDER research, and we want to foster engagement and collaboration across CDER and beyond the CDER boundaries.

The benefits of portfolio oversight are these, and in the interest of time I won't go through each one of them, but obviously, a key activity is there is a lot of interest from the Executive Committee of CDER to do an in-depth review of our research portfolio.

The function of the RGC is more of a consultative body. We still expect the offices within CDER to have the bulk of the management, the budget, the funding, the overseeing of the projects, and the function of RGC is to connect and facilitate and to advocate and to provide consultative advice when requested.

In summary, all of the CDER projects are being linked now, whether intramural, extramural, consortia, et cetera. Outcome measures were collected through -- we developed a five-year plan, and this would allow RGC to address research-related progress going forward.

With that, I am going to go into the second piece which is the NCTR funding submissions. They basically come in two flavors. There is the NCTR funding submissions that

go into the Manual of Procedures and Policies, so we have NCTR submissions that come in, and this is something that is totally separate from the RGC. These activities are managed and administered out of the Office of Translational Sciences. We receive these submissions either directly from NCTR or through the Office of Management. We forward these to the appropriate CDER offices, and we get feedback and review information on whether or not it is of relevance to CDER's mission.

The second aspect, as Dr. Slikker mentioned yesterday, are the scientific reviews of NCTR concept papers. This is a short synopsis of projects of interest. We have a committee, the SPARC committee, Science Prioritization and Review Committee, which reviews these concept papers. Some of these actually make it to full protocol submissions and go through another cycle of review. Those are the two primary mechanisms.

For the first one, there is sort of a heartbeat to it. The process starts sometime around February with a final analysis in the main timeframe. We receive the submissions, as I mentioned, and then distribute those among -- primarily there are five main offices within CDER that address research-related projects. The feedback and ratings come back and we aggregate those within the OTS

leadership and provide that information back to the Office of Management.

The other aspect is the concept paper and protocol reviews. These come on a rolling basis throughout the year. The SPARC committees meet on a monthly basis and it's just a round-the-year endeavor. But the final decision -- there is a time period between January-February and we have a project manager assigned to this activity who organizes the review committees and gets feedback and questions that maybe need some answers. In cases that the committee feels that they don't have the proper expertise we seek out subject matter expertise and further reviews, and complete that process through a SharePoint procedure and communicate that information back to NCTR.

A couple of collaborations and reviews actually were mentioned yesterday. FDALabel -- this is in conjunction with the Office of Translational Sciences -- provides customizable search capabilities for over 100,000 approved labels using structured product labeling tools. CDER medical officers as well as pharmacologists, chemists and toxicologists continuously use this tool in doing labeling reviews and it speeds up the process tremendously, so it is a huge asset to have.

The second one also was mentioned yesterday, the

Smart Template System, which supports CDER reviewers doing the IND review process. It standardizes the input of data into structured templates and provides access to historical data at your fingertips through a dashboard. So that is tremendously useful and a very practical, fully searchable database used to inform regulatory review and decision-making activities. It is very useful also to have access to historical information.

Two tox studies here as examples that we have with NCTR: to better understand the opioid exposure and effect on the developing fetal brain and nervous system by looking at exposure outcomes, et cetera. The second one is more comprehensive characterization of induced pluripotent stem cell-derived human cardiomyocytes model.

Just to show the importance of the collaborations we have with NCTR, just looking at our FY2017 data call reported collaborators for CDER, NCTR by far has the highest number of collaborated projects with CDER. This slide you should all be familiar with because it comes right out of your NCTR annual report. Again, it highlights the number of projects listing collaborators with CDER by NCTR, so, 68 is by far the largest number of other centers within FDA.

We have NCTR/CDER expertise exchange. This is

just a selected few that I wanted to point out of obviously very close collaborations, which we hope to expand going forward, and that would be facilitated through the RGC. I think that is the last slide.

(Applause)

DR. LEIN: We have general discussions scheduled after all the Center presentations, so, in the interest of time we will move to the next presentation which is from the Office of Regulatory Affairs, Selen Stromgren.

(Audio difficulty)

DR. LEIN: The next presentation will be by the Center for Food Safety and Applied Nutrition, Jason Aungst.

Agenda Item: Center for Food Safety and Applied Nutrition

DR. AUNGST: Thank you. I appreciate the opportunity to speak on behalf of CFSAN. These slides were prepared for a previous meeting where Susan Fitzpatrick, our chief toxicologist, was going to come. I think she had a conflict then, and Antonio Mattia, who is a chief scientist in the Office of Food Additive Safety, was going to come but with re-scheduling neither one could make it today, so you’re stuck with me.

I am going to start with an exciting collaboration, one started back in 2011, to give you an

idea of one of the projects we are working on, one of the collaborations, and this is with DARPA, Defense Advanced Research Projects Agency. The goal of this collaboration was to, one, develop quicker effective screens for drugs, food additives, cosmetics, dietary supplements, everything we regulate while, at the same time, reducing reliance on animals.

The importance of collaboration is in the style and how it was set up, and the importance of including the regulatory scientists at the beginning. We heard a lot about this yesterday, about having that regulatory scientist, the one doing the safety assessment, the risk assessment, being involved early on so we can identify the data gaps and streamline our way to getting the system prepared and into use.

Here is a picture of the first product from this collaboration. It’s a liver on a chip. This microphysiological system is meant to be a screening tool. It is made of two cells right now. That way we can screen bacteria, chemicals, whatever we’re looking for. It is currently being tested with a known list of hepatotoxins so we can see what the predictivity is compared to the *in vivo* data we already have. In the future, we are looking at maybe adding a few more types of kidney cells to these and

developing more organs on a chip -- for example, on the kidney, liver, lung, intestine -- and maybe even immunocompetent cells back into these chips so we can have more human relevance or more predictive capabilities.

This partnership was a private-public partnership and included academic institutes who would receive the funding from NCATS, part of the NIH, which is National Center for Advancing Translational Sciences. And another important part of this collaboration was that these academic groups, once they developed the chip, had to market it, they had to make it publicly accessible so we could get it out to everybody and everybody could test it and maybe use this as a way to speed up the validation process and make it more standard across all groups.

A lot of the principles that went into that collaboration were incorporated in FDA’s predictive toxicology roadmap, and we heard a little bit about that earlier today. It was released a little over a year ago. The ideas in there were that the FDA sought viable ways to foster the development and evaluation of emerging toxicological methods and new technologies, as well as to incorporate these methods and technologies into regulatory review.

CFSAN is one of the groups chairing efforts on

this toxicology roadmap, and this roadmap promotes a few general ideas that are important to us especially at CFSAN, and things that we are going to work on here as well. Some of those ideas are internal training in new methods and concepts, so, having more training for our regulatory review scientists so they know what is out there so they can see the stuff that we saw yesterday and think about how these can start being incorporated into a regulatory review system.

Of course, increasing communication early in the development of new methods and alternative methods; increasing public-private partnerships and streamlining that validation or even using a qualification process to get these methods into the regulatory system much more quickly.

This is the framework for incorporating emerging predictive toxicology methods and regulatory reviews. It is from the FDA roadmap. It generally reiterates the principles I just mentioned here. We want to start developing methods to directly address regulatory data gaps. We need to have increased communication, effective collaborations, strong oversight and, of course, transparency in the entire process.

FDA had a public hearing to solicit comments on

this roadmap and I am just going to bring up two comments that really stood out to us. One is we heard that guidance drives innovation. If FDA puts out guidance, if FDA makes statements, that really pushes the science a certain way, so we, as the agency, have to be very clear and very specific about what we are saying, and we need to be much more vocal about it, too. We also need to have better internal and cross-agency communications and sharing, and these are two things that CFSAN is working on as well.

CFSAN has taken the lead for the agency in the implementation of the Tox21 Strategic and Operational Plan which has a number of areas of focus. Number one is to develop and deploy alternative test systems that are predictive of human toxicity and dose response, so this is looking at more than just the high throughput systems we have heard about for years. This is looking at new screening platforms, the microphysiological systems that we have been talking about the last two days.

Number two is to address key technical limitations of current *in vitro* test systems; for example, adding metabolism back into those high throughput systems so we can push more towards human relevance of these *in vitro* systems.

Number three, curate and characterize legacy *in*

vivo toxicity studies to serve as a resource for interpreting Tox21 data. That is very important. At CFSAN we have a lot of data. Weida was just saying how much data we have that he would love to get his hands on. I will talk about one of the projects we have in a little bit where we have done exactly this, going back to the *in vivo* to really characterize what we can get out of the *in vitro* systems.

Four, develop a framework for efficient validation of Tox21 approaches. Like I said, we need to make this much faster; it can't be the three-year validation process that we normally see. And maybe using some different methods -- for example, qualification of use where we could target specific uses of a system.

Five, refine and deploy *in vitro* methods for characterizing pharmacokinetics to increase predictivity and reduce uncertainty, and using *in vitro* pharmacokinetics to combine with *in vitro* tox screening studies we have to give a little more predictivity, making a better case for use. I see it the other way as well. It may even be used in *in vivo* pharmacokinetics with these screening tools, maybe in the future replacing some of the traditional *in vivo* studies that we have conducted.

ICCVAM, the Interagency Coordinating Committee on the Validation of Alternative Methods, this group puts its

purpose right in the title. CFSAN has taken the FDA lead in this 16-federal agency organization. The goals here are, again, to push reliability, reproducibility and relevance of any new methods and new alternative methods. Again, we push to keep those regulatory scientists involved from the very beginning of development.

The communication, collaboration and commitment, these are three C's that run through all these roadmaps. CFSAN strongly supports all these. Also, in supporting our predictive toxicology -- There are two other projects CFSAN has taken on here and one is re-evaluating our current test systems, seeing if we can make these a little better and more efficient. The other is to look at new and emerging technologies.

There are two projects that we have been working on under the idea of re-evaluating the current studies that we use. One is with dog toxicity studies. CFSAN has a very large database of studies, for decades, with animal data, and in one of our projects we went in and pulled out all the dog studies that we had previously seen and took a look at how these were incorporated into each risk assessment that was conducted.

What we found is that often the dog study is not used as the pivotal study for studying safety level;

however, it does contribute a lot of supporting information in a safety assessment. We presented this recently, and our feelings were that we might be able to go without having dog studies or move away from any future dog studies, but the goal would be to look for new methods, new ideas, new concepts and ways to get that same type of supporting information into a regulatory assessment.

The second project was to look back at the rodent bioassay. This is a very long, extensive study. Fred loves to do those all the time. But we need to re-look at this. It is very time and cost-intensive. CFSAN has a partnership with the Society of Toxicology to put on a colloquium series every year looking at new types of research and new science and bring that into the regulatory sciences to let them know what's going on in the field. Last month we had one on the rodent bioassay and we brought in groups from industry, from government and academia to talk about ways we could either redefine how we use bioassays or alternatives to doing bioassays. We heard a lot of different approaches on how certain groups are getting to the cancer risk without having to go through a two-year study.

Those are two projects that we are continuing to work on.

The second topic was developing or looking at new methods for regulatory assessment. The one we have been working on in our research center at CFSAN is the C. Elegans model for developmental neurotoxicity. We have been using this primarily for testing with metals because, as we heard yesterday, arsenic and other metals are a concern for CFSAN through contamination into children's food. We have had promising results with this model. The whole test lasts four days, which is much shorter than most developmental neurotox studies that we have, and the data matches up pretty well with what we have seen with *in vivo* developmental neurotox data in the literature and in other rodent studies.

ICCVAM has taken notice of this and they plan to run a 20-compound blinded qualification study to test the predictivity for developmental neurotox on this system.

Another project we have is the Chemical Evaluation and Risk Estimation System, or CERES, and this sounds similar to some other projects we have heard of in other centers. The idea was that CERES was created to address technical challenges in food ingredient processes in the Office of Food Additive Safety by consolidating all the data in one place and bringing them under a standardized vocabulary.

Like I said, we have had decades and decades of studies and we brought all that information into one place and consolidated it, and this is a system I use every day and my teams use every day in their regulatory safety assessments. Now that we have all that data in one place easy to access we have also partnered with different groups to help build predictive models and included that in our CERES program, and we have a lot of different chemoinformatics capabilities now.

We have another private-public partnership, our collaboration with Altamira and Molecular Networks. Using the data from CERES, FDA data that has already been reviewed and evaluated, they have built models off of that, and the models they have so far are listed here. My team uses these. I really enjoy it. It is very easy to go in and just pick out a chromap study of micro-nucleus for a new compound that we have by low exposure and try to predict what is the potential for carcinogenicity or genotoxicity and then move from there and see what we need to do. We are building a lot more models in the other informatics programs into this system.

I should mention, too, that it started in OFAS but we are looking to expand it through all of CFSAN so we should eventually have dietary supplements, cosmetics,

everything that CFSAN handles in this.

Another important method listed in the predictive toxicology roadmap is use of Read-Across, which uses data from a data-rich or a substance or category of data-rich substances for a data-poor substance that is considered similar enough to use the same data as a basis for assessing safety.

Along those lines, we have a technology transfer agreement with Underwriter's Lab for a project they're calling REACH Across, which is using Read-Across to build predictive models. So far, they have models mainly related to acute toxicities and mutagenicity, and they also have one that they are developing for developmental and reproductive tox, and that is where CFSAN comes in. We are going to provide samples of compounds and data we already have to test their models to start the validation process.

Also within our center we have been working on updating the Cramer classes for a decision tree and we are calling it Expanded Decision Tree. The idea here is that we have a team that went back and looked at the Cramer classes, removed some of the non-structure based questions, increased the scope of Extended Decision Tree to address majority substances and foods, so we have gone from three Cramer classes up to six. This is by increasing elements

and functional moieties, modes of action, species differences.

This team built their database out of about 2,000 different chemicals from over 180,000 studies. I should say the European Union as well as the Center for Alternatives to Animal Testing at Hopkins have both showing strong interest in this Expanded Decision Tree.

On the left is the original Cramer decision tree and on the right is the one we have worked on to expanded out to give us a good screening or prioritization process for looking at a variety of low exposures for chemicals. We see this as being very important for us especially in places where you have like dietary supplements and botanicals, where you don’t have just one chemical; you might have 100 different ones, and which ones do you start looking at and which ones might you not need to do any testing at all. This would be very good for screening some of those that are non-toxic and bringing to the forefront the ones we really need to go after.

CFSAN has also been working on some risk and exposure analytical software. We have FDA iRisk 4.0. The idea is that you can put in some of your own data and the models are already built in that will give you information on potential microbial chemical hazards in foods and health

burden on a population. And there is at-risk which is similar. And FARE-NET, which is a nice program for trying to calculate dietary exposure to nutrients, food ingredients and contaminants, you can take that data and put it back into your iRisk program.

Like I said, these slides were prepared a while ago and recently we heard about some new research studies at the Perinatal Health Center of Excellence and CFSAN has received two of those awards. One for looking at pregnant and neonatal implications on pharmacokinetics for fluorinated alkyl substances, a very new topic, has a lot of initiatives throughout the U.S.

The other one we heard about yesterday is looking at systemic exposure from contaminants or chemicals in tattoos, so we are looking forward to getting started on those with help from NCTR. Thank you.

(Applause)

DR. LEIN: Thank you very much, Jason. Again, we will hold questions until the general discussion period and we are going to try and go back to the presentation by the Office of Regulatory Affairs.

Agenda Item: Office of Regulatory Affairs

DR. STROMGREN: Thank you. I apologize for not being in person and I thank Donna for making a one-time

exception for me to still be part of the meeting. I just wasn’t able to find anyone to take care of my kids this week.

I followed Donna’s initial instructions for what to cover in this presentation. I have the regulatory mandate of ORA. ORA is currently over 5,000 people large, and of course its mission is to protect the consumers and enhance public health by maximizing compliance with FDA-regulated products and minimizing risks associated with those products. It has a very regulatory-focused mission.

About 75 percent of our workforce are inspectors and investigators who are out there on the road every day visiting firms, inspecting firms, collecting regulatory samples and so forth. Twenty-five percent of the workforce, about 1,000 people, comprise the scientific part of ORA. These are our laboratories, 13 of them distributed across the nation and supporting different testing program areas, supporting different product centers. And, of course, we have a headquarters staff leading the field of laboratory workforce.

My office is the Office of Regulatory Science, which is the laboratory component of ORA. All the laboratories are part of our office. All the management and oversight of the laboratories was recently centralized with

the ORA restructuring that happened two years ago. Specifically, my office is charged -- the headquarters portion of the office is charged with developing the scientific technical stuff at the laboratories, provide leadership and manage the resources of the laboratories and help them fulfill their regulatory mission.

Within Office of Regulatory Science we have sub-offices to take on the management of 1,000 people geographically distributed across the nation, requiring our office to stand up a robust management structure and different sub-offices dedicated to different areas.

The office that I am in charge of is called the Office of Research Coordination and Evaluation, ORCE. It is the first time an office was stood up in ORA that is formally dedicated to oversight and leadership of the research conducted at the ORA laboratories.

For ORA, of course, research has a very specific meaning. It is very applied. It is mostly methods development and validation activities to support our regulatory testing needs. Again, about 10 percent of the laboratory personnel is actually dedicated to research; they are 100 percent research personnel, as opposed to just doing programmatic testing. My office is in charge of providing oversight and leadership to this especially

research-dedicated workforce.

In addition to the research emphasis my office also is in charge of the quality system management of the laboratories. Again, all the ORA laboratories are ISO 17025 accredited. Each lab has a quality system manager and we have a national quality system manager in my office that works with the local laboratory QSMs to make sure all our quality principles are adhered to and our accreditation standards are of course upheld.

Slide 4 goes into a little bit about some of the responsibilities of my office. The reason my office was created, and one of the top priorities of the ACRA at the time when she sort of designed the new ORA realigned structure was elevation of ORA science. My office is dedicated to that purpose, so, opportunities such as this for me to be able to present to you sort of goes to fulfill that purpose, bringing some visibility and transparency to the scientific activities of the ORA laboratories.

My office, of course, is also responsible for defining new areas of work for the ORA -- I am using ORA and ORS labs interchangeably; they are part of our office so we sort of switched to calling them ORS labs -- bring new areas of work, introduce new technology, expertise and continuously expand the scientific portfolios of the

laboratories to remain mission-relevant and forward-looking, cutting edge and versatile. Some of the testing we do in some of the program areas have been the same type of methods for many years, so there is a need to modernize some of these testing paradigms, and it all, of course, starts first as applied research method development and then gets transitioned into regulatory testing.

Establishing a framework of harmonized processes that define criteria for a generation of scientific publications, external presentations, scientific contracts and agreements, research proposals -- so, basically a review function, review of all scientific products coming out of the laboratories, coming out of the ORS and scientific enterprise. Again, there was not really a formal process for that before, and I know this is a very important process at the centers requiring many levels of approval and so forth, so we are trying to establish a similar rigorous review process to make sure scientific products that come out of the laboratories represent the best science.

Scientific-based career development also falls under my office. We manage the ORA peer review process, again, focused on recognition of scientific accomplishments. I have already mentioned our quality

system management dimension.

Actually, since I created this presentation, Dr. Paul Norris, who is our office director, has made a decision to also add technical training of the ORA's laboratory staff to the ORCE portfolio, so our name will probably change to ORCET, adding the "t" to reflect that additional scope.

I just wanted to summarize some of the accomplishments we were able to carry out in the area of research coordination and evaluation. We currently use a research proposal tracking tool to gain some visibility on the various research projects pursued at the laboratories. A gain, being a lab network geographically dispersed, we have to put that much more effort to preserve that connectivity to our researchers out in the field.

This research proposal tracking tool is a very important tool for us. It is CARS, Component Analysis Research Tracking System. It was originally developed by CFSAN. This tool has always been around but, again, there was not a consistent use of it so we have sort of revitalized, re-emphasized the importance of this so we can track -- first, we can provide oversight on which research is pursued so we can give direction if something is not quite mission-relevant. We can redirect those proposals and

work with the laboratories to find proposals that really fulfill our regulatory analytical gaps.

Also, of course, with this tracking tool we can track the lifecycle of a project and make sure that closeout reports are generated so that we can see what impact has resulted from that particular work.

As I mentioned, one of the things we work hard at is promoting that sense of ORA research community. Again, everyone being spread across a large country, we have to work at that. We have instituted an annual ORA research meeting and we conducted the first one this past June which was received pretty well.

As I mentioned before, scientific review is an important function of the office so we are working on instituting a master review process. Again, different centers have their own review approval processes. We are looking at utilizing the SharePoint platform to achieve some sort of automated submission, automated assignment of the scientific products to subject matter experts for review and automated tracking of the approvals and so forth. This is being stood up as we speak up to now, so we have been in existence almost two years.

We have been doing this via email, and as you can imagine it is very difficult. We have so many people

submitting so many different kinds of scientific products and a small headquarters office trying to track it all, so we are looking forward to implementation of this automated master review process.

On the next slide I just wanted to show sort of a graphic visual for what areas of work our labs are engaged in, especially in the research and method development applied research fronts. Our labs are specialized along regulated product lines. We have food and feed laboratories that conduct research in that area. Blue is the color for that on the next slide. Green will represent medical products and tobacco-related work. And purple is cross-cutting program.

The writing may be too small, but just for a visual, we have eight food and feed programs. Some of the physical laboratory locations actually support two programs. We call them split labs. They may house both a food and feed program and a pharmaceutical medical products program. Again, in the food and feed we have active research in veterinary drug residues, color food additives, metals testing, filth, food microbiology, mycotoxins, toxins of fungi, persistent organic pollutants, pesticides, so a whole slew of chemical contaminants.

Radioisotopes in foods is a unique program area.

We have sensory decomposition testing, total diet study -- that basically is the survey kind of work that looks at what a typical American family is ingesting through the foods they eat, what sort of chemical contaminants. Allergen testing. Dietary supplements is a big area sort of dual-headed between CFSAN and CDER, and nutritional analysis.

In the pharmaceutical area, compounding pharmacy-related work, a lot of sterility testing; we have a cooperative research development agreement with USP. That's a big area. We do monograph modernization for them. Drug chemistry testing, so, quality testing, potency, uniformity of drug and so forth, microbiology. Metals testing also in the pharmaceutical area.

Response to adverse events, outbreaks, more of an investigative analysis. Shelf-life extension program looking at the repository of drugs the country has to save the public against a biothreat, extending the lifetime of those drugs so they don't have to be recycled all the time which would cost a lot of money.

Spiked active pharmaceutical ingredients in dietary supplements is a big program area, has a high violation rate in fact. I have talked about sterility.

Device radiological health -- some of the work we

do with CDRH is listed there. And tobacco products, of course, we work with CTP on providing analytical methods for enforcement of their rules.

These are just some of the principles that we as an office have been working with the labs to emphasize. For us, what is good science? We want people to think of these very basic fundamental questions as they put together research proposals. What is mission-relevant work and what is the impact? These are the principles that guide our approval.

Slide 10, what is good science. These three basic principles are what we discuss with our research community. Unanticipated challenges -- When you encounter them, please be flexible to redirect the project instead of doing the same thing over and over again expecting different results. And this is sometimes hard to do because people really get married to a certain path of action that they really would like to work. So we want people to exercise that mental flexibility to be able to redirect projects.

Not having a preconceived conclusion, of course, is an important one to preserve objectivity. And negative results are results; they are not that it didn’t work. They are results and should be reported. And, of course, not giving into pressure of time, but properly validating and

reproducing the results. And I know reproducibility of results is actually a topic that has been discussed at the agency level. The science council, I think they have an effort to look into that.

Those are the principles we want people to think about as they do their scientific work. These are some of the specific topics that can stimulate new research. Anticipating future needs and current risks born from advancing technology. So, new products, we always have to be on the lookout for them. As products get more complex our methods to asses them need to evolve as well because now there could be new risk aspects associated with these complex formulations, so we need to be able to properly probe those aspects.

New manufacturing techniques such as continuous manufacturing and 3-D printing -- we need to think about what do we test of the products produced on these. New scientific techniques for product characterization and development, *in silico* modeling -- we talked about this at the alternative toxicology roadmap public meeting. Organs on a chip, *in vitro* biomarker testing, and of course new regulations and policies that may precipitate the need for new methods.

This is some of the new work we have brought in

working with the centers to expand the portfolio of our laboratories.

The last segment of the talk I just want to highlight some areas of current collaboration and intersection with NCTR. ORA has founded and is leading the Interagency Workgroup on Sunscreen Operations Laboratory Analysis and Research (SOLAR). We have NCTR represented on that group. It has actually been a successful group and we have had lots of interesting discussions trying to figure out, working with CEDR as they are working on a new sunscreen policy, what methods we need to have in our repertoire to be able to test these products in conformance with our policy.

In nanotechnology, we interact with NCTR especially. Our nantotechnology group is at Arkansas Laboratory co-located at the same campus as NCTR. We have interacted with NCTR through our involvement with the Prenatal Health Center of Excellence and Alternative Toxicology Methods Roadmap.

There are actually three projects we are working with NCTR on. We heard this at the AI meeting. NCTR scientists are trying to develop an algorithm to actually recognize filth and decomposition in various products. They are working with a filth group at Arkansas. Their algorithm

has actually focused on beetles, being able to recognize beetles from microscope pictures.

We are also working with NCTR in the dioxin versus inorganic pollutants area to automate the evaluation of the data. There is lots of data generated as part of that testing program, so, to first of all decide whether the data is of high enough quality to be included with the larger dataset that is being automated, working with NCTR statisticians.

And we recently started a new interaction with NCTR with the statisticians and bioinformatics group trying to develop an automated laboratory information system, sort of a continuation of our LIMS effort, which has been a bumpy effort.

The last section is potential areas of future collaboration with NCTR. We want to interact with NCTR toxicologists more on the toxicological assessments to inform methods development efforts on novel analytes of interest. When we start a method development effort the first question is always what are the method specs we are trying to meet, and method sensitivity on those specs ultimately go to the toxicity questions, at what levels this compound is going to be toxic dangerous. That sort of dictates a lot of the target method specs.

And establishing collaborations for ORA labs can leverage the NCTR analytical tools and expertise to be integrated into research on fundamental topics. It is a very general area; I can't really think of any specific examples. Actually, recently we did reach out to NCTR. Working with CFSAN we have a need to provide some asbestos testing, so we tried to tap into some SEM and TEM microscopy expertise at NCTR.

I thank you for your time and attention.

(Applause)

DR. LEIN: Thank you, Selen. Given that Selen is calling in we will take any questions or comments for Selen and we will come back to the rest of the group during the general discussion.

SAB members, any questions or comments? Any questions or comments from the center representatives?

DR. SLIKKER: Selen, this is Bill at NCTR. Thanks so much for taking part today. I just wanted to go over some of these opportunities. Certainly, the work that we are doing with your group on the nanotechnology center, which we share and both support, is really important to us, so I appreciate all your activities there and your group's activities to maintain that facility and to keep those studies moving through.

Also, I was really interested in hearing your concerns about asbestos and other kinds of products, and maybe we can help both from an analytical side and from a tox testing side, so we are happy to work with you at any time on some of these new issues that are emerging. Thanks very much for taking part today.

DR. STROMGREN: Thank you very much.

DR. LEIN: That will conclude the Office of Regulatory Affairs presentation and we move now to Center for Tobacco Products. This will be Dana van Bemmel.

Agenda Item: Center for Tobacco Products

DR. VAN BEMMEL: Good morning. It is a pleasure to be back in Little Rock. I am Dana van Bemmel, I am the Branch Chief of the Research and Knowledge Management Branch in the Office of Science at the Center for Tobacco Products. I want to just take a minute to address Bill's comment yesterday about my change in position just to give a little context.

I realized this morning that some of the centers didn't realize that our Deputy Director for Research, Dr. Cathy Backinger, retired from the FDA last fall, and as part of her retirement our office director, Dr. Matt Holman, decided to do some restructuring within the Office of Science. He brought on Dr. Deidre Lawrence Kittner to be

his new deputy and he created the Research Branch and hired me on as the Branch Chief.

What that means for how we interact with the various centers and research is that Cathy had really been the head of the research program in her deputy role, and now I share that role with Dr. Kittner. Primarily, I am coordinating and managing the research portfolio which includes what we're doing here with NCTR. So, Bill, although I may not see the development of the concepts and the protocols, I am now the person signing off at the end, so I am still actively involved.

In addition to that change in our structure, I will just put in a note to anybody who might be coming to the D.C. area that our office moved off the White Oak campus to a beautiful building in Calverton in November, and it really is a beautiful building and it brought together the Office of Science. At White Oak we were split up between a couple of different buildings across campus and now the Office of Science is together in one building and it's fantastic, so I invite any of you who are there to come and visit us.

With that, I would like to just take the next 15 minutes or so to provide an update on the Center for Tobacco Products, the activities that have been keeping us

busy over the last year and a half, and then touch on the research portfolio and the program that sits within my branch and some of the work that we have been doing with NCTR.

I think most of you are familiar with our center but for those of you who are new, just briefly, we are still the new kids on the block at the FDA. The Center for Tobacco Products was created in 2009 so we are almost 10 years old. We initially, as part of the Tobacco Control Act, were charged with the regulation, manufacture, marketing and distribution of cigarettes, cigarette tobacco, roll-your-own and smokeless. And then in August 2016, FDA finalized a rule to regulate all tobacco products. What that means is that we now are able to regulate electronic devices such as e-cigarettes, e-cigars and vape pens, tobacco, pipe tobacco products and really any future tobacco products that may come to market.

Unlike the other centers you have heard from today, the Center for Tobacco Products regulates on a population health model that is slightly different than the other centers because we know inherently that tobacco is not safe, so we can’t be regulating based on the FDA’s traditional safe and effective standards. We really look at what we call this public health model. Our regulatory

actions are based on understanding both the risks and benefits to the population as a whole, and that includes those who use tobacco products and those who do not.

Just to give a little context on the types of research that we do, I feel it is always good to touch on the types of activities that are within our regulatory authority and those that are not because tobacco policy and regulation at the state, local and federal levels has been around for some time and it can get a little confusing.

The Tobacco Control Act gave FDA the authority to regulate the things listed on the slide, and I don’t need to read through each one of those, but it includes things such as product standard development, adverse event reporting, development of health warnings and regulation of advertising and promotion, setting restrictions around those.

Some of the things that CTP does not regulate and therefore cannot fund research in these areas includes things like setting tax rates for tobacco products, setting clean indoor air policies, regulating tobacco-growing policies, providing cessation services. Although we can support research looking at behavioral changes that include cessation, we can’t fund providing them specifically. And changing the minimum age to purchase tobacco products. And

I will say that these are all things that come up very regularly as we're talking to the research community and the community as a whole as to why isn't the FDA doing something in these areas. We, by law, cannot.

Now I will take a little time to talk to you about what we have been doing in the last year and a half or so. This is just one piece of what we do within the Center for Tobacco Products, but it has been a big focus.

In July of 2017, the Commissioner announced our comprehensive plan for tobacco and nicotine regulation, and this plan really placed nicotine at the center of the issue of addiction, at the center of our regulatory efforts. It acknowledged that while highly addictive, nicotine is delivered through products on a continuum of risk with the most harmful delivery of nicotine through smoke particles.

It envisions a world where cigarettes would no longer create or sustain addiction and where adults who still want nicotine could get it from alternative sources. So it is really meant to strike a balance, an appropriate balance, between smart regulation encouraging innovation of products that can help adults who want nicotine to get nicotine from less harmful products while decreasing the likelihood that future generations will become addicted to cigarettes.

Some of the milestones over the last more than a year are highlighted on this slide, and again, I won't read through all of them. I am going to take some time in a few slides to talk about the March 18th publication of three advance notices of proposed rulemaking. In November there was draft guidance on the modification to compliance policy for certain deemed products including flavored electronic nicotine delivery systems, flavored cigars and flavored little cigars and restriction on sales and locations.

I will note, as many have, that these slides were prepared several months in advance. Just last week the Commission announced -- it was published on March 13th I believe -- there was an additional draft guidance published. It is really meant to focus and advance the policies around youth prevention really working towards preventing access to and appeal of flavored end products. I won't go into a lot of detail on any of these but if you are interested in any of these actions they are all listed nicely on the CTP website.

Now I would just like to take a few minutes to walk through some of the advance notices of proposed rulemaking, not just because these were big initiatives within our office but because there were key pieces of information being asked that related to toxicity and

toxicological methods, and so I wanted to highlight those for this group just to give you a sense of the kinds of research in this area that we fund and that we are looking for comment on.

As I noted, in March of 2018 the Center for Tobacco Products and FDA proposed three advanced notices of proposed rulemaking. They are all closed for comment now. The first was tobacco products standards for nicotine level of combustible cigarettes, the second was the regulation of flavors in tobacco products, and the third was the regulation of premium cigars. Within each one of these advance notices for ANPRMs there was a request for additional information and, in some cases, research or data related to specific topics. I will just take a few minutes to talk through some of those.

Related to the ANPRM for tobacco product standards for nicotine levels in combustible cigarettes, FDA was seeking comment on whether the product standard should cover any or all of the following, including combusted cigarettes: roll your own tobacco, some or all cigars, pipe tobacco and water pipe tobacco. And really within the scope of this ask was a request for information on available data related to the toxicity, addictiveness and appeal of tobacco products.

As you will see in the next few slides, we have funded a number of research projects with NCTR to try to address some of those, but clearly there is always room for additional building of the evidence base to help inform our regulatory activities.

The second ANPRM that I just wanted to take a moment to touch on is the regulation of flavors in tobacco products. Within that ANPRM we highlighted that toxicity may result from chemicals formed when flavors are heated or burned, and we were looking for studies or information related to toxicity or adverse health effects from the use of any of these tobacco products. We noted within the ANPRM that there is evidence showing a link between repeated inhalation exposure and adverse respiratory health outcomes.

In addition, it was noted that several flavor substances or compounds may be generally recognized as safe (GRAS) for certain foods; however, authorization for food does not necessarily translate into safety in a tobacco product. Therefore, thinking about toxicity as it relates to inhalation or oral ingestion or exposure is important in understanding potential toxicity or health risk related to tobacco products.

As part of this conversation and plan for

nicotine regulation, the Commissioner and our center director have talked about this roadmap for a healthier future. You will see on the slide that it really highlights several of the issues that I noted in walking through the ANPRMs. It includes publishing product standards that reduce addictiveness, toxicity and appeal to prevent addiction; averting initiation and encouraging cessation among teens and adults. It includes issuing foundational rules to increase efficiency and transparency of the product review process for the industry. It encourages innovative, less harmful and satisfying non-combustibles for adults who still want nicotine. And it addresses the role of all therapeutic products including the performance of medicinal nicotine products in order to help more smokers quit with help.

I should note here that in January there was a public hearing that FDA held to look at medicinal therapy options among youth and young adults. That was I believe led by CDER with CTP, and information on that is also available on the web.

Now that I have kind of given you a sense of the types of regulatory activities that we have been involved in -- this is just one slice -- I would like to take a little bit of time to talk to you about research program

and our portfolio.

I joined the Center for Tobacco Products in May of 2011. We started funding research in fiscal year 2010, and you can see that in 2010 we had just a handful of research projects, and by 2018 we have more than 250 active research projects funded by CTP funds. This includes a large collaboration, which is highlighted in the top part of the bar, with NIH. We collaborate to fund research through the NIH Tobacco Regulatory Science Program, so they administer and manage the grants and we fund them, but it is specific to tobacco regulatory science and it has been a fantastic collaboration.

We also work through contract mechanisms, which I think is no different than any other center here at FDA. We have also had a strong collaborative relationship with NCTR over the years. You can see that the number of projects has ebbed and flowed a little as priorities and resources have changed over time, but, at the end of the talk I will highlight our current active NCTR projects. I will just say it has been a real pleasure working with NCTR and I look forward to future collaborations and continued work.

Finally, we work with CDC. We do have a few collaborations with other centers that I didn’t pull out here on the slide; they are actually in contracts. We have

done some work with CDRH, for example, but in comparison to these other larger buckets -- this is what our portfolio looks like.

And unlike some of the other centers, we don't really have our own intramural programs, so we don't have our own labs. At CTP we do some of what we call in-house research or secondary data analysis, and certainly our scientists are involved in writing and publishing manuscripts and other publishable materials.

Our research projects cover a breadth of categories. These are eight primary research areas of interest. They have not changed over the last several years. You will see that toxicity and carcinogenicity is a large part of our portfolio. And as we begin to work with this changing tobacco market, it sort of makes sense that this is where our dollars would be falling, these newer products.

We cover a wide range of tobacco products. I won't spend a lot of time on that other than to say, based on everything I shared with you in the earlier part of the talk, it shouldn't be a surprise that cigarettes and e-cigarettes are our top areas of research interest, but we try to fund research across the breadth of products that we regulate or that we think may come for review.

I would like to touch on two initiatives that are part of our research portfolio. We have a longitudinal cohort study called the PATH study that has been in the field for more than five years now. It has been a fantastic study with a number of publications. It is really an over-sampling of adult tobacco users and youth.

The second that I will highlight briefly is the Tobacco Centers of Regulatory Science. The first round of these was P50 grants or center grants. We had 14 across the country. They were extremely productive and really a pleasure to work with. Overall, just the centers alone published more than 250 manuscripts related to tobacco regulatory science that we are using to inform our regulatory activities, so that has been fantastic. This past fall we funded what we are calling 2.0, and 2.0 includes nine centers now funded as cooperative agreements.

Finally, I didn’t feel it was necessary to go through all the details of the projects that we are working on with NCTR because the divisions did a nice job of touching on them yesterday, but I will just say that at this point I feel like we have focused our research areas with NCTR in a couple of different core areas or buckets.

We have the inhalation work that we’re doing in rodents, which is a very strong collaboration that has come

a long way. It has been a pleasure to see. Then we have the 3-D modeling that was talked about yesterday as well looking at 3-D tissue modeling and exposure to tobacco smoke. And we have done a lot of work with modeling.

Right now those are our three active areas, but I did bring along several colleagues to join me on this trip and so we are going to spend some time discussing future collaborations with NCTR after these meetings.

This is our research area of interest around toxicity, and that is published for all those interested in applying to our funding opportunity announcements.

And I will just end by saying thank you. I know I have said it several times, but I truly have enjoyed the work that we do with NCTR. Not only has it been good, solid science but it has just been a real pleasure to work with all of the folks down here at NCTR. So thank you.

(Applause)

DR. LEIN: Thank you, Dana. We are now scheduled to take a 15-minute break, so we will reconvene at 10:10.

(Short break)

Agenda Item: Center for Veterinary Medicine

DR. ALLEN: -- Donna especially and Bill Slikker for inviting me. John Graham was the Office Director for Office of Research. Some of you may remember him. He was a

toxicologist by training, and he used to come to this meeting every year and raved about it, and this year he said I would be going in his stead. He is happily retired, driving his -- I guess he calls it a third-wheeler or RV around the country with his wife, so he is having a good time.

I want to just briefly tell you about the Center for Vet Medicine. Some of you who are not from FDA may not even realize that we regulate animal drugs and animal feeds and feed additives for animals.

We basically have five offices, Office of Management, New Animal Drug Evaluation which is a user fee organization similar to CDER, Office of Surveillance and Compliance, Office of Research and we have a vacancy there because John is leaving, and Office of Minor Use and Minor Species which many of you, probably even those in FDA, don’t know about. Real briefly, the Office of New Animal Drug Evaluation is concerned with evaluating animal drugs for approval, and some of you may not realize that we do have the same high-quality standards for approving animal drugs for safety and effectiveness as on the human side. We don’t, though, have the three-phase clinical trials, as CDER does. It is basically the premarket side of our operation.

We do a lot of harmonization with European countries, Canada and Japan in terms of drugs that are approved for companion animals and livestock. As I said, it is driven by the user fee program, so we call them our rich cousins. We are in that area very involved with emerging technologies. We have -- I think the last count was something like 17 or 18 applications for stem cell therapies in dogs, and we don’t have any approved stem cell products for dogs or for any animal, for that matter.

Our key initiatives -- let me just give you a bit of an overview of the center. The key initiatives are modernization of food and feed safety, and that is part of the FSMA, the Food Safety Act. Antimicrobial-resistant strategy is another key initiative, and that is led by many in our center, not just Pat McDermott from the NARMS program, but there is an AMR committee within the center that basically drives our AMR efforts.

As I said, the premarket animal drug review is largely the ONAD component, emerging technologies, which is not just ONAD, Office of New Animal Drug, dealing with all these incoming products that are genetically engineered animals or stem cell therapies, but we complement that in our Office of Research. We have a stem cell biologist. Actually we have three now, and that is relatively new.

When I first got to Office of Research maybe five years ago we really weren't doing any stem cell, so we have really got a department, if you will, or at least a team.

And then the part of the center which you may not hear much about is the Office of Surveillance and Compliance. They are sort of the police of our center. But we do have animal drug adverse events reporting structures. We work closely with ORA if we need something to be inspected. And since they don't have user fees, they are one of the less well-funded parts of the center, but I hope it is changing.

I think Dr. Gottlieb has paid some attention to our center and recognized the needs that the Office of Surveillance has to help uphold the other end. After the drug is approved, what happens to it if we start getting problems with the drugs or applications of the drugs?

You probably have heard about AquaBounty salmon. It was the first genetically engineered animal that was approved by the center years ago. It was approved but then there was an import alert put on it in the U.S. so it couldn't come in from Canada. You may have read recently, a couple of weeks ago, that that import alert was lifted. So, despite the protestations of some senators from Alaska primarily, now the import alert has been lifted and those

eggs from the facility in Nova Scotia will be coming into this country. Whether it will be consumed by U.S. citizens remains to be seen. We are doing this step-wise, but that was something that was recently in the news about our center.

The other thing that you may have heard about is there was an outbreak of campylobacter in children that were handling puppies. This is like a little story. I want to tell you how the Center for Vet Medicine is out there and fixes things or immediately can come to the rescue.

The campylobacter was affecting children and some of them were severely ill after handling these puppies. So the CDC got in touch with our NARMS people, the National Antimicrobial Resistance Monitoring System, and they were able to come in on the weekend and do some quick whole genome sequencing and provide some advice to CDC about the best antibacterial product to use for that one child who was very, very ill.

So, with our people coming to the rescue, if you will, deciding what was the antimicrobial resistance nature of the campylobacter, they were able to make some recommendations to the CDC and there was a happy outcome for that. We are closely aligned with CDC and with USDA through largely the NARMS program, but we do other

collaborations with them as well.

We like to say we are the smallest Center, but I think we are battling that with tobacco and NCTR. We are one of the three, I can say with some confidence. We are looking for a new director, as I said, and we are part of the center that is out in the countryside, if you will, in Laurel, Maryland. This is our main lab building, and this is the building we call Mod 1, and that is part of the CFSAN operation. We also have a small lab up here which is our stem cell biology lab.

These are animal buildings. We house right now about 32 heifers. We are about to do a study with penicillin G in residues in those in tissue. We can accommodate swine, pigs, dogs and poultry. We are about 165 acres and we have about 95 staff now, so we have added a few staff since this slide was prepared.

The OR mission is protecting animal and human health by providing meaningful research to support regulatory decision-making about food, feed and drugs. And our vision is that we are the leader among internationally recognized research programs ensuring the safety of feed, animal-derived food and animal health products.

What makes us unique? We provide critical research to support regulatory actions that are protective

of human and animal health. For example, when John Graham came to the Office of Research he decided that we were really going to be more customer-focused. He completely triaged all of our research projects and kept the ones that were directly related to what the Office of New Animal Drugs needed and the Office of Surveillance and Compliance.

For example, the penicillin-G residue study that we are about to begin is because farmers long ago, decades ago, would say that the penicillin-G that they were injecting for mastitis, for example, was not effective at the label dose, and so they started using three, four, five times the label dose. ORA is seeing residues in cattle tissue, usually spent dairy cows, and we know that it is because many farms, although those drugs should not be available to the farmer as of last year, we know that apparently they are telling us that the drug is not effective at the label dose.

The manufacturer of penicillin-G compounds -- there are a couple that are commonly used -- they are not going to do the study to look at what should the withdrawal time be. And so we are starting to do that study to basically help the Office of Surveillance and Compliance when they get these violations, and that is the way John had envisioned the Office of Research. I think that is what

our center Director, Steve Solomon, envisions us to do. We will provide services that the Office of New Animal Drug or the Office of Surveillance and Compliance needs us to do.

There was a recent study with arsenic in poultry feed, and Office of Research did that study and it resulted in the withdrawal of a product that was fed to chickens that contained arsenic. So those are just a couple of examples I can give you of how we see ourselves and how we actually provide a service to not only the center but to the U.S. population.

We can study large animals. We understand the animal drug and feed industries. We have a lot of people who have either worked in industry and come to us or people with experience in animal science industries. We leverage partnerships with other federal agencies, as I mentioned, and regulated industry as well, and universities. We investigate questions that we can’t get grant money for, and we also investigate things that cannot be published or wouldn’t be publishable.

We conduct timely studies and they are all triaged now so we have quarterly reporting out on the progress of all of our studies, and we answer critical questions to facilitate the review of new animal drug applications. We also investigate antimicrobial resistance,

and we detect contaminants in drugs, chemicals and microbiological contaminants in animal feeds and tissues from food-producing animals.

We have a wide breadth of research programs all the way down to the genome level cell and organic systems and whole animal, and we are fully AAALAC-accredited. I don’t know if I have a slide about our quality assurance team, but we are very strong proponents of GLP and we do many of our studies, not all, under GLP guidelines, good laboratory practices.

The subject expertise is very varied. I won’t go through all of these, but you can see that we have a large number -- I guess we have 35 or 37 principal investigators, and these are their areas of specialty. We have the Division of Residue Chemistry that supports ONAD in new drug applications doing method trials. We have an applied vet research program, Division of Animal and Food Microbiology, the NARMS program and Vet-LIRN, which is the Veterinary Laboratory Investigative Response Network, which I will have a few slides on.

I think many of you probably have heard of the NARMS program. It is a collaboration with CDC and USDA to look at resistance in microbes in meat samples from supermarkets. We will monitor the trends in resistance and

disseminate the timely information, and I welcome you to Google NARMS and look at their website. It is publicly available and you will learn a lot about the interactive tools that they now have to help people understand the resistance and changes in antimicrobial resistance. They conduct research and they assist CPM and FDA to make decisions about approval of antimicrobial drugs.

And I will say that this is largely focused on the retail meat. We recently were funded to start looking at seafood, and we also have a partnership, if you will, with our Office of New Animal Drugs, and those scientists are now starting to look at companion animal antimicrobial resistance problems and how that may affect humans.

I am going to go quickly through this but you will have these slides available to you. Right now, in retail meats, we have more than 20 states, and, as I said, we are starting to look at the seafood, largely the farmed fish.

Animal food microbiology -- we look at a lot at contamination in feedstuffs, and we look a lot at animal feeds and feed products that have to do with -- one example is the distillers' grains which are -- antibiotics are used in the distillation process. Those distillers' grains are a byproduct of that process and those are used for animal

feed, and now we are finding that some of those antibiotics used in the distilling process are showing up in animals. That is why we focus on that.

Residue chemistry has national milk residue monitoring. We are looking at mycotoxins in animal feeds and hormones contamination. In the Division of Applied Vet Research we are doing meats and milk safety. We are doing biomarker research. We are doing work with, as I said, GE animals and stem cell research.

We have a wonderful aquaculture facility and have at any one time a number of species of fish. That work also supports some of the animal drug applications that are coming in through the Office of New Animal Drugs.

The Vet-LIRN investigation really was born out of the melamine crisis with the baby formula in China and then dog foods in this country, and now Renata has over 45 laboratories that are part of her network and they are promoting human and animal health by collaborating with veterinary diagnostic labs around the country. This is a fantastic way to actually identify trends and perhaps outbreaks really early by having this network. She likes to think of this as the CDC of the Office of Research, CVM. She has grants that she helps buy equipment and instrumentation for other laboratories in her network.

Now I will switch to what are we doing with the National Center for Toxicological Research. We have about 14 studies ongoing and I heard just recently that there might be a 15th. Largely, they are involved with, for the most part, intestinal microbiome and antimicrobial resistance in intestinal microbiota, and nanomaterials, and we will be looking at mechanisms of AMR in salmonella.

I will quickly go through this list of collaborative efforts within NCTR. You can see that there is great interest in the microbiome and in human intestinal epithelium. We are looking at the impact of tetracycline on the microbiome. We're looking at, again, the barrier functions of human intestinal epithelial cells, and evaluation of antimicrobial resistance in human intestinal microbiota following exposure to residual concentrations of antibiotics.

And we are very interested in working with CFSAN and the rest of our colleagues at FDA looking at, in our case, a gut on a chip, not a liver on a chip, model, and these are, again, in the early stages but we are collaborating with Carl and others on this project. We hope to be moving forward with it in the next year.

Steve Foley is the PI on this project of salmonella enterica virulence and we have three co-

investigators at the Center for Vet Medicine.

And Tong is here, and he is working on three or four projects down here, some of them on nanotechnology. This is the other area that you are interested in, looking at analysis tool development and working with Steve Foley.

Here is another one that Tong is involved with, which is looking at human cell lines, looking at high throughput genotoxicity testing. This is a new collaboration with NCTR with Tong -- mutagenicity of nanomaterials with whole genome sequencing of mammalian cells.

And this is evaluation of cadmium in nanoparticles as a positive control for *in vitro* assays toxicity. And this is, I believe, our new one -- studies on the intrinsic structural multidrug efflux pump looking at AMR salmonella enterica and that role in antimicrobial resistance.

I quickly went through the collaborations that we have at Center for Vet Medicine with NCTR and I didn’t mean to give it short shrift, but I hope that when we have time for questions and answers -- we have Steve Foley here and Carl from NCTR -- hopefully we have time for some Q&A on those projects. Thank you.

(Applause)

DR. LEIN: Thank you, Mary. We will move right into our last Center presentation for the morning which is from the Center for Devices and Radiologic Health, and this will involve a WebEx of sorts, so we will cross our fingers that it works.

Agenda Item: Center for Devices and Radiological Health

DR. MARGERRISON: Good morning, everybody, and apologies for not being there in person. It has been a crazy week here but I hope everyone is having a good week and I shall just plow on. I would like to give just a -- I think this is similar to some of the stuff I said last year -- just a bit of an overview of what we do at CDRH and the breadth of products that we classify. And then, along the lines that Donna and Bill and I talked a few months ago, suggest some ways that we can make even tighter the great connections that we have at CDRH between us and NCTR.

The CDRH has purview over a very broad number of products and not just on the device side, and I will give some examples of those in a minute. But we are also responsible for *in vitro* diagnostics, so we have a clear link there with our colleagues at the Center for Drug Evaluation and Research, particularly as it relates to companion diagnostics for a lot of therapies which require

concomitant drug therapy as well.

We also have purview over devices that emit radiation, so that includes not just some more medical things, which we will go through, but also we have legal jurisdiction over things like microwaves and cell phones. We obviously don't actively regulate things like that. In the case of cell phones we could probably talk about it for the rest of the day, but actually most of that responsibility lies under the FCC's jurisdiction. We do have the legal requirement to monitor published information and advise the FCC on appropriate radio frequency levels of emissions from cell phones and other devices.

Broadly, we are a pretty busy center. We actually look over nearly 600,000 individual proprietary brands on the market now. We get about 1.5 million reports back on how all of those products are acting in the market. There are 18,000 device manufacturers who are registered with us, and they actually control 25,000 manufacturing facilities worldwide. And, of course, we have to inspect those where appropriate to ensure that they are conducting manufacturing of devices to appropriate quality standards so that we know that those devices are appropriately used in the U.S.

We have about 1900 employees, and I usually joke

that this is about one-third of the number that Caesar's Palace employs, and as a center we say that we couldn't even run their kitchens, which is probably true, but we do get 22,000 premarket applications per year. Most of those are what we call 310K, so they are low to medium-risk devices. They typically don't require a lot of clinical evaluation before they can be marketed. They are relatively straightforward things that we have seen many times before. We also have a number of what we call Class 3 devices which are significantly higher risk, but I will give some examples of each of these as we go on.

We just announced last week that most of CDRH is reorganizing. My office is not; we stayed out of the reorganization, but the rest of CDRH recently reorganized. I think it is quite interesting because, instead of having an artificial divide across offices between pre and post-market, for example, and compliance, we have put all those into a single office. They look after different areas of medical device technology. They are responsible for those products right from the very start, the first submissions or inquiries that we get from manufacturers, all the way through to post-market and inspection of manufacturing facilities. This is actually going to lead to an enormous amount of improvement in processing times and things like

that.

Certainly, one of the things that we have realized as a center is that the number of applications that we are getting is going up a lot each year, and, clearly, our budget and our head count is not going to go up at the same rate, so we can't just throw resources at the sort of problems that we have. But, to increase our responsiveness and to make sure that we are meeting our user fee targets and deadlines, we are going through a major exercise of effectively what industry called 20 years ago business process re-engineering, so we are now organized predominantly along the type of medical devices that we oversee.

For example, the top three actually are relatively easy to remember because they go from the head downwards in the body, and then we have the neurophysical medicine office, ophthalmic CNT, orthopedics and surgical. We also have a seventh overall office which looks after -- it is the equivalent of our Office of In Vitro Diagnostics and Radiological Health. That remains pretty much intact.

Let me give just a few examples of some of the things that we oversee and then I am going to propose a way that, as I said, we can get even closer to NCTR which I think will benefit both of us.

The first one, *in vitro* diagnostics, is a very large area for us. We have seen a lot of these sorts of examples -- glucose monitors, which are absolutely vital for diabetes; companion diagnostics I talked about a little bit. But we are looking at some of these things a little differently now.

A lot of the genetic tests now we are trying with a lot of these areas to show that companies have a sufficiently good quality system, sufficiently good oversight of what they are doing that we can allow them to use the same technology in a much more simplified version to get further tests out there, and “23 and me” is a pretty good example of that. We have had many discussions with them over the years, not all of them fruitful, but we have actually arrived to a place where we have a very good understanding of them and they have a good understanding of us. Actually, a lot of their technology and their controls and quality control over that is extremely good now. So we are getting on with them extremely well.

I wanted to mention on this slide as well one of the things that has changed very much for us as a center over the years is that devices can now also not just incorporate but actually be software. We call those SAMDs, software as medical devices, and that is an extremely

interesting area. There is much that was said about software as medical devices in the 21st Century Cures Act that was signed into law in December 2016 that really helps us define what is a device when it comes to software.

A good example of that is an app that is actually built into the Apple watch that can -- we have known that a lot of these things can measure heart rate for quite some time, and the apps are getting much more sophisticated nowadays and they can start thinking about diagnosing atrial fibrillation and things like that. So, as they move towards getting much more diagnostic, then they become much more likely to be regulated by us as a device.

There are two things to note about that, I think, from my perspective. The first is where apps and things or anything else is diagnosing conditions that we consider to be lifestyle or general wellness -- for example, your BMI could be considered a general health indicator rather than an indicator of a specific disease -- those are not software devices. The other thing to note, unlike what was written about at great length in the public press, CDRH does not regulate the Apple watch. We regulate, in some instances, the software and apps that could be put on the watch, but that was a great theme with much of the national press.

Moving along from devices, just to give you a brief rundown of radiological health, I think some of the interesting things we have here is that we are actually responsible -- and the last bullet there, the Mammography Quality Standards Act -- we are actually responsible for a lot of the mammography clinics as well as the devices that they actually use. I think it's a bit of a quirk of the legal history.

Our big areas of business in this sort of area are MRI and CT scanners, and a lot of the research that we do internally within my office at the center is looking at, for example, deep learning algorithms that can be used in CT scanners so that you can effectively get much better images out of a CT machine using worse data, and worse data means lower dose. So we are doing a lot of work on reducing the dose that especially pediatric patients might encounter when they have a CT scan by using much, much better algorithms. And we do a lot of research in this area and all of those algorithms actually go public through GitHub.

Laser safety is something that is very important for us as well built into a lot of medical devices, of course. But we also are pretty active really on the consumer side of lasers as well. Many laser pointers, particularly of a certain wavelength, can actually carry

different wave lengths of light with them, which happens to be just a fantastic way for wave lengths to enter the eye and then actually get focused on the back of the retina. So we actually have a group of people who look at a lot of those.

They are typically the ones that are not manufactured in the U.S. but in other countries and they can come in. You can buy them off eBay and everywhere else on the Internet, and very often those are the ones that are causing severe problems when, for some obscure reason, people shine them and try and get pilots as they are landing at airports. That is actually a real concern.

I will try to summarize a little bit. We have recently over the last year undertaken an exercise to try and get a bit more specificity around our priorities, which I am going to go through, but we are also trying within my office to align a lot better with what our major targets are and our regulatory science priorities, and I think it is very pertinent to the discussion at this meeting.

We have traditionally been organized along very much a divisional line along disciplines and things like that. We are in the process of changing that right now to be much more aligned to our offices of health technology through the reorganization of the rest of the center and,

also, some of the things that are of particular interest to us as a center in our major priorities. I have listed some of those here.

One of the big themes that is coming out from the Hill this year as it relates to devices is safety of devices, and the other things that we want to start trying to promote from an innovation perspective are pediatric devices -- big problem for healthcare, really, because many pediatric devices, particularly implants, tend to be reduced-size versions of the adult ones, and that is not necessarily appropriate. And it can be very difficult for manufacturers to put a lot of money into the development of pediatric devices. The numbers very often just don’t add up. So we are trying to work out a way that we can stimulate innovation in these areas.

Very much women’s health remains a key focus for us as a center. We are also beginning to get somewhere now with our medical device development tools that I want to say a few words about. In the same way that Center for Drugs has its drug development tools, we are beginning now to start seeing the qualification of a number of medical device development tools, and in the next month or two we are going to see the first two or three that have come out of OSEL and CDRH itself. And those are not just

standardized methods but they can also be actual tools; for example, phantoms that are used in the assessment of radiological scanners and things like that.

Our purpose here is really to eliminate a lot of unnecessary questions from premarket applications, specifically because if we have tools and methods that we have qualified as being regulatory grade -- whatever that actually means -- if a sponsor uses that tool then we don't have to start asking them questions about how did you do it, what did you do, how did you make it. What we can do instead is just look at the summary report and say that's fine or it is not. Our review is to focus more on the important questions and not on the ones that really aren't that important in terms of how precisely a particular assay was done.

I have actually set my people within my office a competition to see which team can get the first one qualified and after that to the general public. There have been at this point two patient outcome measures that have been qualified as tools and one biomarker, and, as I said, over the next couple of months we will get the first ones out. I am imagining that the first one to be qualified in our areas will be an ultrasound phantom for use with newer high intensity therapeutic ultrasound devices which are

becoming increasingly useful for removal of fibroid and tissue debridement non-invasively.

Computer modeling and simulation remains a key research interest for us. We are increasingly seeing that that is taking a much larger role within the regulatory framework as well. As I said, safety is a massively important area for us as well.

I have listed here -- and you will be glad to know there is no test at the end of this -- very broadly our 10 top-level regulatory science priorities. What we have been doing over the last 12 months is to put some specific objectives around each of these because they are necessarily very broad. For example, leveraging big data for regulatory decision-making. That is so broad that anything can fit within it. We have been spending a lot of time putting some more meat on the bones, if you like.

The two of those that are particularly important for our interactions with NCTR that we feel we need to take a more top-down approach on -- and this is something that I find particularly important because many research projects within the government, which is not my background particularly, come from a very bottom-up approach -- there are lots of incredibly clever scientists who have lots of great ideas. What we are trying to do within CDRH is to

take a more strategic top-down approach, and, specifically as it relates to NCTR, the two really important ones for us are to get better at biocompatibility -- and we have a lot of efforts going on under there -- but also to reduce healthcare-associated infections, particularly with endoscopes and duodenoscopes and things like that.

On the next slide, the three specific areas on biocompatibility that I want to explore with NCTR broadly are to look at test methods, and where can we get test methods better for chemical characterization, et cetera, for things like *in situ* curing material to, obviously, advance alternatives to *in vivo* testing wherever we can, and to try and help us define chemical equivalence, which is one of the big areas that we issue deficiencies in premarket applications.

The last is we need to get a lot better understanding the reprocessing of a lot of multi-use devices, scopes being an obvious example, and not just having decent protocols for that but actually understanding what happens in the real world in the clinic. And the age-old problem that the whole industry has been facing for an awfully long time is what can we do about biofilms -- prevention being better than cure -- but if you do get a biofilm what can we do about that.

So I am essentially proposing that we take a fresh look at this between NCTR and CDRH and say, okay, we now have a common understanding of the big picture; let's actually put together a whole program for addressing, even if it's just a small area of that, to try and address one thing well rather than lots of thing a little more piecemeal.

I am obviously happy to answer questions if that is appropriate.

(Applause)

DR. LEIN: Thank you. I think we will start with any questions or comments for the current speaker. Any from the SAB? Any comments or questions from the center representatives? Bill?

DR. SLIKKER: Glad to hear from you today. I was just thinking about the work that you're doing with 23 and me and many of these other groups. This is an area of which quality assurance is something that we have really invested in in terms of omics technologies, and so that is a good topic for our Division of Bioinformatics and Biostatistics to work with you -- I'm sure we already have to some extent -- to work on this together to try and figure out what is the best way to make sure that we have quality data coming from these various kinds of genomic instruments that you

are responsible for.

DR. MARGERRISON: I couldn’t agree more. That is becoming more and more important, especially as it relates to a lot of the next-gen sequencing that we are dealing with now. Really, so much depends on those things and finding the right patients for the right therapy, whatever that therapy is. That is really vital. I think the whole area of data quality and data validation is essential.

It is allied as well with the next initiative that we have, which very much we are part of but not driving, to really start having a nationwide registry of how devices are used, like the CDER Sentinel program. If we can understand that, then we can just continually improve things and make them better and better.

I absolutely agree. I think once we are over the current wheel we should look at that in more depth, without a doubt.

DR. SLIKKER: The other thing, just briefly, Ed, is of course you are aware of the Perinatal Health Center of Excellence funding a study with your group on noise levels of MRI that is used in children, and so it gets to this point of making sure that the equipment and processes that you are responsible for are being evaluated thoroughly. So I appreciate you guys submitting that and I

think that is going to be an interesting study.

DR. MARGERRISON: I think it will be. When it was first recommended by our MR group I looked at bit querying at them because I didn't quite get it, but it is very interesting because anyone -- and I'm sure there are many in the room there -- who has had an MRI, you realize there's a lot of noise. We have headphones on, but unborn children hear that, and that is really becoming more apparent now. And I think it's a great example of where devices or anything else can get designed and we don't necessarily take into account everyone who might be affected by them. It is a fascinating area, and we are thrilled to be part of that new Center of Excellence. It will be great.

DR. SLIKKER: And the final thing is just about sterilization of medical devices, et cetera. This is something that our Division of Microbiology has worked on over the years, and I know you probably have already been working with them, but I just want to reinforce that we are very willing to work with you on that kind of issue looking at those sterilization processes.

DR. MARGERRISON: Actually, that's an area that I think we need to expand, to be absolutely blunt. I think with certainly what has been happening with some of the

ethylene oxide processes, there is one in Illinois that has been shut down for -- I won't go into the reasons. That is not appropriate for this meeting.

But one of the things I think we need to think about is can we investigate other ways of sterilizing things to an appropriate level. It is a huge issue, but at the moment the industry is extremely reliant essentially on ethylene oxide and gamma, and if something goes wrong there are no alternatives to turn to. And the capacity issue is a big problem for sterilizing all those devices. So I think that's an area that we need to look at really closely and see if we can move the needle a little bit on that.

DR. SLIKKER: Thank you, Ed.

DR. LEIN: Are there any other questions or comments around the table? Thank you very much, Ed. We appreciate you joining us by phone today.

Agenda Item: Discussion of NCTR Research

DR. LEIN: That brings us now to the discussion of NCTR research with the SAB members. This is a wide open forum for SAB members to ask any questions of the center representatives and for the center representatives to ask any questions or make comments to the SAB.

Starting with the SAB, any comments or questions?

DR. ASHNER: Michael Ashner, SAB. I have one

general question maybe for all of you. One of the themes that came across in some of the presentations was the *in vitro* alternatives, and I was wondering if there is sort of a task force that is overlooking the efforts that are done by each of the centers and many other actually federal agencies. EPA is one of them. Or is this done basically within each of the centers individually?

DR. MENDRICK: This is Donna. As Denise mentioned, we formed an *in vitro* systems working group across the FDA and we are looking at alternative assays, and part of this is looking at what is being done within FDA. One of the subgroups is looking, for example, at what we are doing with MPS and stem cells, but eventually we are going to expand to other types of alternative assays.

DR. ASHNER: I am aware of a lot of work that has been done in EPA, for example. I think they can benefit from what you are doing and *vice versa*. I was wondering if there are any interactions between those two agencies.

DR. MENDRICK: Yes, because of Tox21. For example, I recently presented to Tox21 the work we are doing in MPS systems, so we do have communication. And we have talked in the past via Tox21 about a number of alternative assays we are doing.

PARTICIPANT: And, Donna, ICCVAM is another

opportunity for interagency conversation.

DR. SLIKKER: And just to add to that, Micky, you are probably aware that FDA, NIEHS and NIOSH are all members of the toxicology program, and that program has regular scheduled meetings, and Gonzalo is a member of that. Denise also sits at the board as well as myself. And on those occasions we get a chance to talk about these collaborative efforts that go across, and usually EPA and others are at the table, but certainly those three groups, NIEHS, NIOSH and FDA, are represented there, and that is our role, is to help coordinate those kinds of activities.

So the roadmap that many people have mentioned within FDA over the last year, year and a half, has really been helpful in getting out the word about the cooperativity we want to see between these various agencies.

DR. STICE: Steve Stice, SAB. This is a general question for all of you. Thank you for your presentations. It was helpful for me to understand some of the interactions between NCTR and your centers, and that really helps us.

I did hear a lot about the different projects that are going on between your centers, and I wanted to ask what is the outcome that you are looking for as far as a

project being successful? Is it publications, is it changing something fundamentally in how it's done at your centers? I just wondered if there are metrics that you use to determine whether something is a success.

And I understand this is research and most of the time things don't work out exactly how you planned, but I would like to hear a little bit about the metrics that you are using for a successful project.

DR. WILSON: This is Carolyn, Wilson, Biologics. We developed a system of metrics based on four general areas: one, is it relevant to our regulatory mission. The second is scientific dissemination which means is it being published in the scientific literature that's peer reviewed, is it being presented at relevant scientific professional meetings, that kind of thing. Sometimes it is also perhaps being presented at our scientific advisory committee meetings in the context of product reviews.

The third is scientific impact, and that is where we are really distinguishing just dissemination from really the uptake of the information by the scientific community or regulated industry. So it might be the use of a model we develop by a regulated industry, for example.

And the fourth area is really what you were saying, which what is the direct impact on the regulatory

actions in the form of perhaps being reflected in our guidance documents or other regulatory practices that we have a variety of ways to evaluate. Those are much longer-term shifts that may take years to really see something come from the laboratory into a finalized guidance.

But I will say that all of our research scientists are also what are called researcher/reviewers, and so the knowledge that they gain in their research program also is reflected in their daily interactions with sponsors just in terms of the kinds of questions and advice that they give sponsors.

That's it for my center.

DR. RUIZ: Juan Ruiz, CDER. Very similar to what Carolyn just mentioned, we have developed a series of outcome metrics. At this point in time they are basically weighted equally. Two of the most important ones are dissemination of information whether by presentations or publications, and the second one is informing guidance. We are also looking very closely in terms at impact that the research has on speeding up the review process. We are very much concerned for providing tools to center reviewers to accelerate product reviews.

DR. VAN BEMMEL: Dana van Bemmel, Center for Tobacco Products. I will just echo that we have an

evaluation program that is very similar to my colleagues' in that we are looking at similar outcomes across the entire research portfolio. But I think it is fair to note that it's different than what would be a traditional outcome perhaps from an academic project where you're looking for a publication. Many of our projects don't ultimately end in publication, so spend a lot of time looking at alternate outcomes and, through this evaluation, white papers, internal referencing, whether papers that are published are submitted to the docket, those kinds of things. So we try to be more encompassing in what those outcomes and evaluation look like.

DR. ALLEN: Mary Allen, Office of Research, Center for Vet Medicine. We are similar to what Carolyn described although not quite as far along as we would like to be. We basically want to know if it answered the question that was posed, whether it was posed from outside of CVM or within CVM. What impact did this research have on industry, on regulation? Was there a specific regulatory impact, was there a guidance that resulted or guidances that resulted?

And I will also echo that many of our studies are not publishable because they relate to proprietary information. We are not penalizing our scientists because they are peer reviewed, so, the numbers of publications in

a peer-reviewed journal is not the only measure. If they have published within CVM a final report, a white paper, those are all credited to the scientist, so that we make sure that if they are doing good work they will be rewarded for that if they are going through the peer review process.

We have been looking at research impact over the last year. We have had one person sort of dedicating part of his time to trying to find measures to look at what we use for research impact measurements. I think that is going to be critical to basically inform not only our center but the FDA and outside the FDA of the impact that we can have. Thank you.

DR. HINTON: Mine is just a brief comment because I echo everything that the centers have said. But I think one of the important things that you have heard from each of them is what the RIA would be, the research impact outcomes, as measured in each of the individual offices.

But I think one of the important things is it’s coming together collectively as a group, which is what we do through the Office of the Chief Scientist in the various working groups to be able to understand what each group is looking at, what each one is doing and be able to share that both internally and externally.

DR. SLIKKER: To follow up really on Denise’s

comment, this is really a challenge for the agency because oftentimes, except for meetings like this, we don't really talk about the research that's being accomplished between the centers. Not only that, but then the outcome of that is really difficult for someone in the laboratory to understand unless we have information back to us that says, oh, we used that as part of a guidance, or we used that to inform another study, or we used that in some capacity.

And so, one thing that Juan and I and his colleagues at CDER have been talking about is how can we make sure that we communicate something about the progress of the research that you have looked over and agreed was important to FDA. When that research progresses over the next two or three years, how do we get information to you to make sure you understand it has been done, and then how do you give information back to us by saying oh, yes, we used that, by the way, Bill, to do X, Y or Z.

So that challenge is really real because it doesn't happen immediately; it happens over time, and it means we have to keep communicating, and people turn over and projects change, et cetera. So this is something that we really need to work on and I think that all would agree that better communication across all the centers would be very helpful here.

DR. FELTER: Susan Felter, SAB. My question actually ties into the challenge that you were just describing, Bill. My question is around the research tracking program. Juan, you talked about one that CDER has and I think we also heard about a research proposal tracking tool that is now in the Office of Regulatory Affairs which originated from CFSAN.

So my first question is whether the research programs in which NCTR is actively involved, are those reflected in the tracking programs of the different FDA centers, and are they easily searchable so that you could search across the FDA centers to see which ones NCTR is involved in and who the PI is, that sort of thing. Because it seems like that is a great opportunity for that kind of dissemination and maybe tracking progress and ultimately knowing how the work done at NCTR is influencing regulations or decision-making that the FDA centers have.

DR. WILSON: In CBER, I think you raise a really good point. I would say it is probably somewhat uneven as to how it’s reflected in the research reporting database. We do have a place for our PIs to list their collaborators. Whether or not a PI would list an NCTR collaboration as a project in their research report would vary I think on how much they are doing it versus it’s just kind of NCTR is

really doing it and they are just providing some general advice and guidance. They probably wouldn't report that as part of their research program.

It is challenging every year when I need to figure out what's going on because some of it I can pull out of the database and some of it I can't, so that is something that we need to work on to improve.

DR. RUIZ: The answer for CDER is yes, because we are very intimately involved in reviewing many of the protocols and proposals that go through and get funded. We have initiated these annual data calls. The caveat here is that, again, these are self-reported outcomes. Typically, we have a CDER collaborator with NCTR and it behooves the co-investigator to update results of that project. It takes a lot of work because you have to stay on top of everyone to make sure that they in fact comply with the updates and whatnot. Some people do it quicker than others.

We have now gone through two cycles. We haven't achieved 100 percent. We know which are the projects out there that we expect to have feedback. And we just try to communicate to investigators in general and we will make it also well known to the NCTR side that it's in their interest to make sure that these projects are updated.

At the end, we will be analyzing results and

creating reports. Hopefully, once we have this database fully developed it will be accessible by different offices and hopefully we will have dashboards so that you can extract the information for your particular needs.

DR. VAN BEMMEL: I think we have a slightly different approach in that the research program as a whole within the Center for Tobacco Products is tracked within our branch, the Research and Knowledge Management Branch, so we don't have investigators input it themselves; we have a staff dedicated to doing that. We have a good tracking system, and the graphs that I shared in my presentation are generated from that research tracking system. We are working to develop it out so that we can have access to direct documents, publications, outcome types of documents, as well as any kind of (indiscernible) or IRB, but those types of documents associated.

So we spend a lot of time thinking about that on the front end, and it is very, very useful. But we are not tied to any other center; that is just within our center.

DR. AUNGST: Jason Aungst, Center for Food Safety and Applied Nutrition. At CFSAN we do have an internal tracking system, and we separate these based on where the research is done. If it is research done at the center it goes into our center tracking program, and if it's other

collaborations we're working on with NCTR, there is a program inside the center's Office of Chief Scientist that handles tracking those.

DR. STICE: Juan, I have a question for you. I am really impressed -- north of 40 projects, something like that, that you have with NCTR -- that's very impressive.

In one of your slides you showed the process and I wanted to get a further understanding. It looks like the proposals would come from NCTR and then go over the wall or cross over to CDER for evaluation and then come back with feedback to NCTR. I don't know if that really portrayed the process, or I guess I'm asking how often does it happen where it goes in reverse and goes to NCTR first and then a proposal and then comes back.

DR. RUIZ: There are two flavors to the NCTR proposal reviews that we perform. One is where we are receiving proposals that come from either NCTR directly or from the Office of Management. I cannot tell you the history behind that. I am sort of the new person on the block.

The proposals come to the Office of Translational Sciences. We have a project manager that shares those proposals with the different offices within CDER. There are about five offices that are critical here because they are

involved in actual research. There will be identified a CDER collaborator in those instances.

We then get back from the different offices their assessment of that proposal, and there is a ranking process that goes through. There is a series of questions that we ask in terms of ranking from one to five. At the end of that process we develop just a ranking which we communicate back to the Office of Management. Office of Management has the actual budget allocation. In my group we have a sort of figure that we know of, but is not the exact number, and then the Office of Management, based on the final number, draws a line and those above the line get funded and those below do not.

The other flavor is those concept papers that are submitted on a rolling basis throughout the year, and that is a very short synopsis of what the investigator has in mind. We provide a service. We put together a scientific priorities committee. If that committee feels that they do not have the appropriate subject matter experts, we will ask for that within the center and provide feedback to NCTR. Some of those concept papers will be fully developed into an actual protocol. A protocol is basically a full proposal with details, and then this comes back to this committee which will then rank and provide funding.

DR. STICE: Thanks for that. That sounds like really a very good formalized process. I was just trying to get a feel for how much organic interactions occur where maybe a CDER scientist says, okay, something is happening at NCTR that I am really interested in. Does that happen, and how often?

DR. RUIZ: I don’t have a number but I know that that happens a lot. Just within my group I know that there is a lot of interaction back and forth with specific NCTR investigators. I don’t know the number but I think center-wise with so many offices -- CDER is pretty large -- I expect that there is a lot of back and forth communication.

But certainly we want to improve that. One of the RGC’s remit, if you will, is to foster that collaboration and communication.

DR. ASHNER: Michael Ashner, SAB. This is related, and my question is do you ever use external reviewers?

DR. RUIZ: Actually, this is something that I thought coming in -- I have brought up that opportunity because sometimes it is difficult for us to find reviewers quickly. There’s another project which is to map where the expertise is within the center and the agency more broadly, but I think, my personal opinion is, that we should be able to access the expertise at NIH and other agencies within

HHS.

I don’t know where that lies. I have been told that there are certain restrictions in terms of to what extent, if any, we can access external reviewers, even accessing in academia, for example.

DR. VAN BEMMEL: We can chat offline, Juan, but we do use external peer review for some of our research proposals. We go through the regular government employees for those that might be at NIH. We also use special government employees to look at our proposals. So I think there are mechanisms and ways and I would be happy to chat with you later on about how we have formalized that.

DR. LEIN: Great discussion. Yes, Chuck?

DR. KASPER: Chuck Kasper. I am curious. I know it’s not applicable to all the centers, but is anyone conducting any research on organic foods, considering their increase in popularity and consumption? I thought it would be particularly appropriate -- maybe it’s reverse thinking because you don’t think of organics as having toxicants or less -- but particularly for the antimicrobial resistance.

DR. AUNGST: The label “organic” is under the jurisdiction of the USDA, and pesticides fall under EPA. Not much we can help you with there.

(Laughter)

DR. LEIN: Any other comments or questions from the SAB? Turning to the centers, do you have any additional comments you would like to make or any questions of the SAB?

DR. RUIZ: I just want to say thank you to the organizers for inviting me. This was my first time here. I hope to return in the future. I have enjoyed learning much more detail from the different centers and what's going on at CDER and meeting some of the faces with names.

DR. ALLEN: I would also like to thank the organizers and Donna again. I have learned a lot during this day and a half not only about NCTR but about the fellow participants and colleagues around the table here. It is great to learn in more detail about the nature of research going on in these other centers. I thank the board members for their time.

DR. LEIN: Any other comments?

DR. SLIKKER: First of all, I want to say that the question about tracking is an important one and of course NCTR has had a tracking system for years. In fact, in relation to your question, Steve, we actually have one protocol I am aware of that we actually have a PI from another center. It is not even an NCTR PI. But in many cases, there are co-PIs from the other centers and they

actively take part, including in coming up with the initial idea that is then developed among several centers, certainly two or more. So that does happen routinely.

Also, a lot of things are carried by our dear colleague, who I call our face of NCTR in White Oak, for example, and in the D.C. area, which is Donna. She, by serving on all these committees and being a person at the table, really collects a lot of information and links people up. It's like a dating service for research. She says, well, you ought to talk to so-and-so, and so they start talking and pretty soon a proposal may well come out of that. Not of marriage, but of research.

(Laughter)

It is an important set of connections that we make. But we do it at this meeting too -- and you are responsible for a lot of this -- by asking questions and providing your guidance to link up opportunities not only between NCTR and the other centers but between the other centers themselves. It really is an important process. All of those help in moving that forward.

I just want to take a moment to thank not only our Science Advisory Board members who, as I mentioned yesterday, really drive this process forward. It is very critical that we have that input.

And in answer to your question a little bit, Mickey, 10 years ago we always included an external reviewer on our major protocols. We started moving away from that because we realized that even though we really appreciate all the science and research that the external reviewers bring, the most important question was is it important to FDA. And so we rely now almost entirely on the input evaluation from our FDA colleagues. Besides being brilliant, they really have the concerns of what FDA should be doing at the top of their list. That is important to us. Sometimes we go external with some of our projects, but we oftentimes get what we need from our FDA colleagues over here.

This opportunity, the SAB once-a-year activity and also the subcommittee that I know you volunteered to be chair of next year for Neurotox, all those activities really do drive the science from the other parts of the world, which is the academic part of the world, the industrial part of the world and other government agencies, from time to time as well. We do really appreciate that input and it does drive things forward.

I, of course, want to thank everyone on this side of the table for being here and being part of this activity. Some of you have been doing this for a while. I

can point to people like Carolyn and Dana. And some of you are relatively new at the table but we have known you for years like Jason, et cetera. But the point is that you all bring really good character to the table. You tell us about the needs and aspirations of your centers and how we can work more closely together, so I really appreciate that.

And then, of course, Denise, who helps glue all this together in her role as the Office of the Chief Scientist head. This is really important to us to have here and to have her understand then the relationship between all these centers when it comes to getting research done, so we appreciate your being here very much, Denise.

Just a final thanks to Donna who makes all this happen and has the responsibility as the government person who is informed and running these things according to a very strict, long list of rules, and Kim who works with her and many others that help support her to get this done.

And finally, of course, to our staff that is here who did a lot of the presentations and made this happen, as well as the staff such as Jeff and others that work out the details of how we're going to project and move all this stuff forward.

And finally to Pam. We have already given her a plaque for her service. I'm sure that's going to serve her

well. But I want to tell you personally how much we have enjoyed having you at the helm of this organization helping to lead us forward, and we don't want you to be a stranger but we really do appreciate the efforts that you put in since, believe it or not, 2014 or 2015. It has been a long time ago that you started. We really appreciate your efforts. It has been invaluable to us to be able to move this activity forward and to have someone of your stature really understand and help provide creative solutions to issues that come up when it comes to research throughout the FDA, so thank you very much.

DR. LEIN: And I will just end by saying that we were tasked with three questions and I would like to just give you a brief overview of that before we close the public meeting, since some of this is supposed to be done in the public.

I think that I speak for the entire SAB by, first of all, thanking all of you for your time and your openness and being patient with us with our questions, some of which came out more than once I think. I think that, as a committee, we are all very impressed by the quality of the research that is being done at NCTR, since that was our task, to really review NCTR, but also by the other centers.

I think that since I have the longevity on this

board now I can say that, over the five years that I have been participating, I have seen a real increase in the interactions and communication between NCTR and the centers. That, I remember was one of our early criticisms when I started, that you needed to be more interactive, and I think that is definitely happening.

I really applaud all of you. I know how hard it is to do that, particularly given the size of some of your centers. Just keeping track of what's happening in your own center is challenging enough, let alone interacting with others. So I really applaud you, and I think the rest of the board supports me in applauding you, for the efforts that you are taking to develop various approaches for really keeping track of what's going on and communicating with each other, so, well done.

In terms of horizon scanning, which is the other issue we were tasked with giving you some advice on, we talked a little briefly -- you will probably hear more during the closed session -- you guys are doing what all of us do to keep track of the horizon and what's happening on the horizon, which is getting out and engaging in scientific meetings, having meetings like this engaging with other sectors.

I can't really think of anything additional to

advise you on in terms of keeping track of what's happening on the horizon, Again, I think you are really being proactive and doing a good job of keeping on task with that.

I think the really big issue that we all kind of grapple with trying to advise you on is that your scope and your mission are so broad and you have very limited resources in the context of that mission. So our advice always to you is that it is really important, we think, for you to develop metrics for really evaluating what are the most important questions -- and it seems like you have all developed very good metrics for doing that -- and that you need to focus on how do you allocate your resources to most effectively focus on the most important issues.

And one strategy that I think I haven't heard a lot about and may be something to think about is what is your strategy for evaluating programs to sunset. Obviously, you cannot keep maintaining everything all the time. Priorities are going to shift, priorities are going to change and emergencies will arise, so, how do you shift your resources and really sunset the programs that are no longer effective or no longer needed.

But, overall, I always come away from these meetings incredibly impressed. I am very proud to say that

you are my colleagues, so, keep on keeping on. You’re doing good.

With that, I will end the public meeting. Thank you, everybody, for your participation.

(Whereupon, the public session was adjourned.)