FDA National Center for Toxicological Research

Science Advisory Board Meeting

April 4-5, 2023

These summary minutes for the April 4-5, 2023, virtual meeting of the National Center for Toxicological Research (NCTR) Science Advisory Board were approved on April 13, 2023. I certify that I attended the meeting of the NCTR Science Advisory Board and that these minutes accurately reflect what transpired.

____/s/_____	____/s/_____
Donna L. Mendrick, Ph.D.	Patricia Ganey, Ph.D.
Designated Federal Official, NCTR	Acting Chair, NCTR Science Advisory Board

A verbatim transcript will be available and posted at https://www.fda.gov/advisory-committees/toxicological-research-science-advisory-board-national-center-toxicological-research/2023-meeting-materials-science-advisory-board-national-center-toxicological-research

April 4, 2023. Meeting began at 9 **am (Eastern)**

The meeting was called to order by the Acting Chair of the Science Advisory Board (SAB), **Patricia E. Ganey, Ph.D**., Professor Emeritus, Department of Pharmacology and Toxicology, Michigan State University.

She welcomed the following **Science Advisory Board** (SAB) members and asked each to introduce themselves:

1. **Patricia E. Ganey, Ph.D.,** Professor Emeritus, Department of Pharmacology and Toxicology
2. **Mary Ellen Cosenza, Ph.D., DABT,** President, MEC Regulatory & Toxicology Consulting, LLC
3. **Gregory M. Lanza, M.D., Ph.D.,** Professor of Medicine, Cardiovascular Division, Washington University School of Medicine
4. **Kenneth S. Ramos, M.D., Ph.D.,** Executive Director Texas A&M Institute of Biosciences and Technology, Texas A&M University
5. **John-Michael Sauer, Ph.D.**, Senior Director, Nonclinical Lead, Peptilogics
6. **Alexander Tropsha, Ph.D.,** Professor, Associate Dean for Data and Data Science, UNC Eshelman School of Pharmacy, UNC-Chapel Hill
7. **Cheryl Lyn Walker, Ph.D.,** Alkek Presidential Chair in Environmental Health, Director, Center for Precision Environmental Health, Professor, Departments of Molecular & Cell Biology and Medicine, Baylor College of Medicine

(Michael Aschner, Ph.D., Professor of Molecular Pharmacology, Neuroscience and Pediatrics, Department of Molecular Pharmacology, Albert Einstein College of Medicine, could not join this meeting.)

FDA Speakers Representing the Office of the Commissioner and other FDA Centers:

1. **Namandjé N. Bumpus, Ph.D.,** Chief Scientist, Office of the Chief Scientist (OCS), Office of the Commissioner (OC)
2. **Karen Elkins, Ph.D.,** Associate Director for Research, Office of the Director, Center for Biologics Evaluation and Research (CBER)
3. **Chekesha Clingman-Henry, Ph.D., MBA, CDR USPHS,** Acting Deputy Director for Science, Office of Translational Sciences, Center for Drug Evaluation and Research (CDER)
4. **Michael Eppihimer, Ph.D.,** Director, Division of Biology, Chemistry and Material Sciences, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health (CDRH)
5. **Suzanne C. Fitzpatrick, Ph.D., DABT, ERT,** Senior Advisory for Toxicology, Center for Food Safety and Applied Nutrition (CFSAN)
6. **Dana van Bemmel, Ph.D.,** Chief, Research Operations and Advisory Resources Branch, Office of Science, Center for Tobacco Products (CTP)
7. **Regina L. Tan, DVM, MS,** Director, Office of Applied Science, Center for Veterinary Medicine (CVM)
8. **Sean Linder**, **Ph.D.,** Deputy Director, Office of Regulatory Science, Office of Regulatory Affairs (ORA)

National Center for Toxicological Research (NCTR) Scientific Leaders and Speakers:

Tucker Patterson, Ph.D., Director
Donna Mendrick, Ph.D., Designated Federal Official and Associate Director of Regulatory Activities
Gonçalo Gamboa da Costa, Ph.D., Senior Science Advisor and FDA Liaison Officer to the National Toxicology Program
Frederick Beland, Ph.D., Director, Division of Biochemical Toxicology
Steven L. Foley, Ph.D., Director, Division of Microbiology
Robert Heflich, Ph.D., Director, Division of Genetic and Molecular Toxicology
Laura Schnackenberg, Ph.D., Director, Division of Systems Biology
Anil Patri, Ph.D., Director, Nanocore, Office of Scientific Coordination
Bradley Schnackenberg, Ph.D., Associate Director, Office of Scientific Coordination
John Talpos, Ph.D., Director, Division of Neurotoxicology
Weida Tong, Ph.D., Director, Division of Bioinformatics and Biostatistics

Dr. Ganey (Acting Chair)

- Dr. Ganey opened the meeting and asked SAB members and other panelists to introduce themselves. She provided an overview of the role of the Science Advisory Board and the purpose of today's meeting.

Dr. Mendrick (Designated Federal Official)

- Dr. Mendrick read a statement that assured the attendees that all appropriate ethics regulations were satisfied. There was a request from the Physician's Committee for Responsible Medicine to speak for 5 min during the public comment period this afternoon. On NCTR's website are documents from this group and from the Humane Society of the United States.

Dr. Patterson (Director, NCTR)

- Dr. Patterson provided an overview of NCTR with a summary of NCTR staff and collaborations across the FDA and with outside entities. He provided examples of ongoing studies in support of FDA regulatory centers with an overview of the many projects underway using new alternative methods (NAMs) using in vitro and in silico approaches. He focused on some of the regulatory bioinformatics tools developed to help CDER and other centers. He ended with some hurdles facing NCTR such as budgetary constraints and personnel recruitment.

Discussion Highlights

- Dr. Ganey asked how the budget constraints are set. Dr. Patterson responded that some centers will fully fund a project, but it is constrained by budget year. Some of the projects funded by internal competition also have some restrictions such as not buying equipment. The agency now will fund such competitive projects at the beginning of the next year versus part way through the current year. This will give the researchers more time to spend the funds wisely. Dr. Ganey asked about the Predictive Toxicity Roadmap. Does NCTR have timeline and milestones within the roadmap such as number of protocols? Dr. Patterson responded by saying not in terms of numbers, but we are working with product centers who many times want information sooner vs. later and thus many of our projects are moving to shorter term projects. An example is work being done with CBD where the scientific knowledge is needed very quickly

Subcommittee Review of the Division of Bioinformatics and Biostatistics (DBB)

- Dr. Alexander Tropsha discussed the findings of the Subcommittee Review of DBB that was done in 2022 (the report is posted on our website). He provided an overview of the reviewers and which reviewer was responsible for each focus area and the materials provided to them. Dr. Tropsha described each focus area and their comments.
  There was unanimous approval of the Subcommittee report.

Morning Break 10:28 am-11:00 am

Response to Subcommittee Review

- Dr. Tong, Director of the DBB, responded to the Subcommittee Review via a presentation at this meeting. (His written report can be found on our website.) He restricted his response only to comments within the report that required clarification and further explanation. He answered general questions first and then ones pertaining to the five focus areas of his presentation to the Subcommittee. These areas were 1) regulatory applications and support, 2) alternative methods and knowledge bases, 3) precision medicine and therapeutics, 4) artificial intelligence and machine learning and 5) real-world data and real-world evidence. An example of a general question was how DBB determined project selection and prioritization.

Discussion Highlights

- Dr. Tropsha thanked Dr. Tong for a robust answer and for providing additional details that were not covered in the materials provided for their review. The reviewers wanted to provide suggestions for future research and thanked him for responding. He discussed budget

constraints and hiring issues and asked Dr. Tong how he finds a balance. Dr. Tong stated that he discusses projects with the principal investigators (PI) and noted that the majority within his division are funded externally to NCTR. Dr. Ganey asked about the personnel. Do you need to pass on projects because of limited personnel? Dr. Tong said that postdocs are the greatest part of his budget and, while he has had to turn down a few projects, it does not happen very often and these are usually in the area of support, not research. Dr. Tropsha expressed an opinion that in the next 5 years he will see growing pressure for the skill sets and contributions of this division in the area of AI. He encouraged FDA leadership to help his division. Dr. Walker commented that the area of AI is growing everywhere, and it is important to get in front of this and it will require higher salaries. Dr. Ganey noted that hiring at NCTR is something that the SAB visits every year and maybe they need to find more ways to help.

Statement from the Chief Scientist

Dr. Namandjé Bumpus., Chief Scientist, provided comments on NCTR. She has found her interactions with NCTR to be very engaging and they invite her into their work. She is very enthusiastic about the appointment of Dr. Patterson as Director and expects NCTR to reach even higher heights under his leadership. She introduced her background in pharmacology, personalized medicine, drugs' effects on signaling pathways, etc. For 12 years she was a professor at Johns Hopkins. The Office of Chief Scientist helps to move research into regulatory science and works to stimulate collaboration inside and outside the agency. She noted the Commissioner is supportive of NCTR and she views her role to advocate for all scientists, particularly those at NCTR. She welcomed questions from the SAB members.

Dr. Ganey appreciated her commitment to NCTR and thanked her for taking time to speak at this meeting

FDA Center Perspectives

Dr. Karen Elkins, CBER, described their regulatory mandate and research that supports this. CBER's research programs include vaccines, allergenics, CAR-T cells, etc. Dr. Elkins provided examples of collaborations with NCTR including omic analyses and alternative in vitro models (e.g., microphysiological systems). One omics collaboration involves the assessment of 405 nm light as a tool to pathogen reduction. A modeling interaction is studying immune responses to SARS-CoV-2. A mouse model of CAR-T cell therapy is being developed to help assess safety and efficacy of next generation of such therapies. Together CBER and NCTR are studying the impact of Zika virus infection during pregnancy and are developing in vitro approaches including the use of placental membranes. Potential areas of future collaborations include product toxicity-related topics, reproductive toxicology, omics and in vitro alternative methods for assessment of safety, efficacy and mechanisms of action of CBER-regulated products.

Discussion Highlights

- Dr. Ganey thanked her for the informative presentation particularly regarding the contributions of NCTR. Dr. Lanza asked about the CAR-T cell therapy and noted that cytokine storm is inherent in its mechanism. How are you going to separate toxicity from mechanism of action?

Dr. Elkins said that the model is intended to allow blocking of individual aspects so they can assess the multi-component process.

Dr. Chekesha Clingman-Henry presented for CDER. She introduced herself as she is new in this role and presented the regulatory science research within this center. In brief, their research investments support new tools, processes and information systems to speed the development of new drugs. She provided examples of collaborative projects with NCTR, including the development of statistical tools for regulating deep sequencing based tests, optimization of genotoxicity tests to detect N-nitrosamines, a systems biology evaluation of the immune response in COVID-19 patients, the use of AI methods to identify sex differences in opioid use-related cardiovascular risks and the development of a standard reference test for bacterial contamination of pharmaceutical products. Areas of potential collaboration include toxicity studies on drug impurities, bridging the gap between in vivo animal data and human microphysiological systems, and understanding emerging technologies.

Discussion Highlights

- Dr. Ganey thanked her for the informative presentation. Dr. Cosenza noted that CBER has a collaboration on CAR-T and CDER also works on drugs that operate the same way. Is CDER interested in collaborating on this project as well? Dr. Clingman-Henry believes CDER has some collaborations in such projects and agrees it is important. Dr. Tropsha asked how projects are initiated with NCTR. Dr. Clingman-Henry said that are two methods. 1. Center directed projects that are communicated to NCTR. 2. NCTR-initiated project review process. Both work well but there are some challenges and opportunities for improvement. She is hearing from CDER that they would like earlier and more engagements in NCTR-initiated protocols.

Dr. Michael Eppihimer, CDRH, introduced himself and noted that he is the research arm of CDRH. They produce free products within this center. He introduced CDRH's broad mandate and details on their research arm. They use project management concepts to prioritize the gaps, develop detailed project plans (deliverables, milestone, etc.) and, once protocols are approved, retain these principles to track progress. Timelines for tool development are now 2 years or less. Once a tool is developed a group within the office qualifies it. Along with the publication the project team develops a user manual and a communication strategy. They are using webinars, videos, etc. to enable quick adoption. He ended his presentation with an overview of their regulatory science tool areas and where NCTR can contribute. Their goal is to have 50% of gaps being worked on by other people as they do not have the bandwidth to address all of them.

Discussion Highlights

- Dr. Lanza noted that imaging is moving quickly with AI and soon will do the imaging interpretation for initial diagnosis and longitudinal management issues. What are they doing in this area? Dr. Eppihimer noted that they have 2 programs. One is digital pathology to evaluate the tools (algorithms) to identify abnormalities in tissues, etc. They have a large AI program as well. Dr. Lanza is concerned about the longitudinal management issues and wants to make sure they get the funding they need for this. Dr. Eppihimer said they are investing in this area and do not focus on individual grants but in long-term planning.

Break from 1:15 pm to 2 pm Eastern time

Public comment period. A representative from the Physician's Committee for Responsible Medicine, Joseph Manuppello, spoke for approximately 6 min. He supports NCTR's movement to alternative methods but is concerned funding requested in the 2024 budget will be used for new animal studies. They would prefer evaulation of new alternative methods to human data and not animal. They request that NCTR solicits public comments and track their animal use. This was the close of the public session.

Dr. Anil Patri (NCTR) briefly provided an overview of his Nanocore staff, mission and outreach. Ongoing projects include international documentary standards development and review (funded by NTP and in collaboration with FDA centers, NCI, etc.) and assessment of physical characteristics of nanoparticles on radio-enhancement and DNA damage in cancer cells. Future projects include the development of new test methods identified through stakeholder engagement and a greater understanding of complex multifunctional nanomaterial, gene therapies & vaccines that utilize nanomaterials.

Discussion Highlights

- Dr. Lanza said there is a tsunami of nano articles coming into journals but quality control for what they are making is lacking. Is there a way that the methods you are working on can become more available to CROs and others that make these products so they know how to test them? Dr. Patri noted that they publicize the research via conferences and, once they develop standards, CROs have access to them. U.S. Pharmacopeia is getting into liposome standards as these have become generic products. As the methods and submissions become more complex, they need to engage others. Dr. Patri mentioned that they had organized a workshop for small businesses and that this information is available. They encourage product developers to come to FDA early. Dr. Ganey asked about toxicity assessment of plastic particles. Dr. Patri noted they are working closely with CFSAN on this. They need to know what is in the product that fish, for example, are ingesting. Literature has focused on polystyrene since standards exist. Thus, they need to identify and quantify the agents of concern and thus, they are not conducting toxicity studies at this point.

Dr. Suzanne Fitzpatrick, CFSAN, described their regulatory mandate (e.g., they oversee approximately 90% of the food supply) and provided an overview of some ongoing work with NCTR. These collaborations include work in zebrafish to evaluate inorganic arsenic developmental effects, assessing the performance of 3D-bioprinted human skin as barrier models and multiple projects on cannabidiols. She introduced a project with Johns Hopkins University (JHU) evaluating the effect of metal mixtures and gene-environmental interactions on human brain organoids. Dr. Fitzpatrick also discussed FDA's Alternative Methods Working Group, which she chairs, how this spans all of FDA, the public documents that were generated and the public website of this group to provide transparency. Dr. Fitzpatrick mentioned the Global Harmonization of Food Safety (ILMERAC) and ASPIS/RiskHunt3R international collaborations with both CFSAN and NCTR as members. She ended with a tribute to Dr. Dan Doerge, a retired NCTR collaborator, who was awarded the 2023 Philippe Shubik Distinguished Scientist Award for his toxicology work, most of which was in support for CFSAN.

Discussion Highlights

- A comment made by Dr. Fitzpatrick about the JHU group looking at how their brain organoids "might think" elicited a comment from Dr. Ramos. Dr. Fitzpatrick mentioned that the JHU

group has a paper published in *Frontiers of Toxicology* and clarified that this is not what CFSAN is asking NCTR to do.

Dr. Dana van Bemmel, CTP, presented the Center's goals, regulatory scope, and its new leadership. She stressed that science drives decisions and briefly described their research program. Dr. van Bemmel listed their research priorities which include addiction, behavior and toxicity. She outlined several interests that align with NCTR including toxicity, addiction, health effects and informatics and described three projects in some detail. Dr. van Bemmel described several areas of potential collaboration and ended her presentation with a brief overview of the external evaluation conducted by the Reagan-Udall Foundation. She thanked NCTR for their research help.

Discussion Highlights

- There were no questions for Dr. van Bemmel

Dr. Regina Tan, CVM, provided an update, information on current collaborations and future steps. They work to protect human and animal health and align their research with their regulatory functions. These include safe and effective animal drugs and food additives in animal food. Strategic goals include supporting One Health, advancing emerging technologies and fostering a One CVM culture across organizational boundaries. As an example of the 3Rs, they are using laparoscopic analysis in some animal studies, thus using fewer animals and saving money. (Their targets are animals so they cannot avoid all use of animals.) She presented some examples of CVM's Office of New Animal Drug Evaluation-NCTR collaborations including many in vitro approaches such as studying the performance of 3D bioprinted human skin for dermal absorption of animal drugs. CVM's Office of Applied Science also works with NCTR. One collaboration is studying the structure of the multidrug efflux pump and their role in antimicrobial resistance in *Salmonella enterica.* As a future step, CVM and NCTR will put in place an agreement for inter-institutional animal research.

Discussion Highlights

- Dr. Lanza thanked her for her presentation. He asked how CVM can do toxicology in ruminants. Dr. Tan said that CVM has the ability to study cows and goats but that these food animals do not live long lives. (The study she mentioned above that implemented laparoscopic analysis was done in cows.) Dr. Lanza asked about studies on milk. Dr. Tan mentioned that CVM retains a herd of milking cows so can do such studies.

Dr. Sean Linder, ORA, presented their regulatory mandate noting that they do not set guidances. Approximately 80% of their work force is involved in inspections and the remaining in laboratory work studying samples to ensure compliance. Their mandate includes defensible scientific results, horizon-scanning, a modernized technology base, etc. He presented their research landscape, the number of completed research projects and methods to measure their impact. He outlined three COVID-related investigations including one done in concert with NCTR. Dr. Linder mentioned NCTR's assistance with a novel method for managing lab data generated from geographically diverse ORA labs and their help using AI for the potential development of a detection and evaluation tools for use in international mail facilities. He discussed interactions with NCTR including joint membership on many agency level committees, and ongoing and future collaborations.

Discussion Highlights

- There were no questions for Dr. Linder

Break from 4:05-4:15 pm Eastern time

Presentations from NCTR Research Divisions

Dr. Frederick Beland, Director, Division of Biochemical Toxicology, presented an overview of his division, staff, outreach (within and outside FDA) and the division's mission, goals, strategies and metrics. Ongoing and proposed topics included studies on tattoo pigments, cannabidiols and nitrosamines. The work with tattoo pigments is being done in concert with CFSAN. The cannabinoids studies range from examining their pharmacokinetics and effects on male reproduction and the liver. Work involving nitrosamines is in collaboration with CDER.

Discussion Highlights

- Dr. Ganey asked if the Sertoli cells metabolize CBD and, if not, what does that mean for the study of their toxicity. Dr. Beland thinks they do not and noted that in vivo there is a circulation of such toxicants so direct metabolism may not be an issue. Dr. Sauer asked about its metabolism via phase II. Dr. Beland said they do not know at this time. Dr. Sauer asked a question about the tritiated carbon black study. Dr. Beland said they will be doing some work to determine the stability of this reagent.

Dr. Weida Tong, Director, Division of Bioinformatics and Biostatistics, provided an overview of the division, their vision, mission, goals and highlighted collaborations with FDA regulatory centers. He provided an update on his AI4Tox efforts and announced that Drs. Li and Chen won the 2022 Environmental Mutagenesis and Genomic Societies Bioinformatics challenge wherein they used artificial intelligence approaches to predict drug-induced liver injury and as an alternative to animal clinical pathology testing, respectively. Other ongoing projects include studies into sex differences in adverse drug events and exploration of opioid issues using artificial intelligence.

Discussion Highlights

- Dr. Ganey asked what fraction of projects are initiated by his division. Dr. Tong estimated that 60-70% of the projects have a co-PI from other divisions and centers. Dr. Ganey asked about the studies using female and male hepatocytes as those cells are compromised since they do not come from healthy patients. Dr. Tong responded that they are working with Dr. Albert Li's company using cryopreserved hepatocytes which he believes some come from healthy individuals. Dr. Ganey mentioned that these are still compromised. She encouraged Dr. Tong to find ways to keep personnel at NCTR given the issues of finding new members as he mentioned in his earlier presentation. Dr. Tropsha stated that CDRH's presentation was more suggestive in what could be done with NCTR rather than ongoing studies. What work are you doing with CDRH? Dr. Tong noted that CDRH has a lot of skill in machine learning related to devices. They do have one project to help them with data analysis. He said he should work with them more closely in chemoinformatics. Dr. Eppihimer noted that they have such a project in discussions with stakeholders. Dr. Tropsha asked if they track how your databases are used and how they collaborate with outsiders in these areas. Dr. Tong said they do not track database use in

general but can track how the liver database is used because they can track publications that arise from these data.

Dr. Robert Heflich, Director, Division of Genetic and Molecular Toxicology, discussed the division staff and outreach activities (within FDA, other governmental agencies, academia) and leadership in organizations such as HESI and OECD. He discussed his division's mission, goals, strategies, and performance. Several ongoing projects were presented in some detail. 1) The study of nitrosamine impurities (done in conjunction with CDER), 2) developing new methods for safety evaluation of genetic toxicology endpoints using in vitro organotypic models (in collaboration with CDER and CTP), and 3) updating OECD genetic toxicology test guidelines which involves international outreach.

Discussion Highlights

- There were no questions for Dr. Heflich

The meeting adjourned at 6:16 pm Eastern time

April 5, 2023. Meeting began at 9 am Eastern time

Dr. Steven Foley, Director, Division of Microbiology, provided an overview of the staff, mission, outreach and collaborations with FDA regulatory centers and ORA. Examples of ongoing projects include investigating the effects of nanomaterials against select bacteria associated with healthcare and foodborne infections and an in vitro assessment of compounded triamcinolone-moxifloxacin to determine substance(s) in the formulation responsible for reported adverse events (in collaboration with CDER). Future projects include working with CBER to discover the signaling pathways and mechanisms that contribute to several pathologies associated with coronavirus infections and, with CDER, using intestinal organoid models to investigate excipients incorporated into drugs by nanotechnology.

Discussion Highlights

- Dr. Kaspar asked if they have considered comparing genes between avian pathogenic E. coli (APEC) in urinary tract infection-causing associated E. coli and the potential that APEC may be the source of UTIs since both are extraintestinal in nature. Dr. Foley responded that they are interested in this. Dr. Kaspar asked if they are looking at defining pathotypes for delineating the various strains into virulence groups. Dr. Foley said in the affirmative and added that he works with the Genomics for Food Safety (GEN-FS; a multi-agency group) which is trying to understand virulence of Salmonella and how best to regulate on this. Dr. Kaspar encouraged him to continue to work with USDA as it will impact food safety. Dr. Cosenza asked if his group was involved in the recent eye drop issue. Dr. Foley stated that they were not but said these types of issues led them to develop a rapid respond resource as described by Dr. Patterson. Dr. Cosenza asked about the division's structure and Dr. Foley responded that it is still one large group as it was under the late Dr. Cerniglia. Since he was just recently appointed Director, he is trying to determine if it would be wise to divide the division into Branches although he spoke of a concern related to stopping the current free flow of information.

Dr. John Talpos, Director, Division of Neurotoxicology, discussed his division's staff, outreach, mission, goals and strategies. Ongoing projects discussed included 1) biomarker qualification for the use of T2 MRI for nonclinical neurotoxicity safety studies, and 2) the use of in vitro models to assess the effects of early-life exposure to opioids and cannabinoids on development. Future projects include in vitro assessments of developmental effects of exposure to acetaminophen (in collaboration with CDER) and, with CFSAN, to combinations of heavy metals

Discussion Highlights

- Dr. Cosenza commented on the issues of adverse outcome pathways as it was widely discussed at the recent Society of Toxicology meetings. She applauds him for studying this and noted that it seems to take years to get this done. Dr. Ganey stated that chemicals can affect normal physiology, but this may mean toxicity or adaptation. She cautioned that this could add difficulty when looking at several adverse outcome pathways at one time. Dr. Ramos had a series of questions and comments. He cautioned that using MRI to improve pathology assessments might lead to incorrect conclusions as there are many physiological/biological causes for MRI changes. Dr. Talpos said he is interested in such feedback. Dr. Ramos asked if Olney lesions have been found in humans. Dr. Talpos stated that he has not seen any published reports to date. They are doing such research to see if these are rat-only changes or do occur in large species. Dr. Ramos cautioned them on how the translatability is reported on any of these findings. His last question was on the use of labor hours as a metric. Dr. Talpos stated that this is not an accurate measure at this time but, if it proves to be useful, will require more diligent reporting.

Dr. Laura Schnackenberg, Director, Division of Systems Biology, described the division staff, organization, outreach, metrics, their mission, goals, research interests and strategies. Several ongoing projects were presented and included collaborative work with CDER and CBER on the effects of COVID-19 on pregnancy and prenatal/postnatal development and potential biomarkers predictive of anthracycline-induced cardiotoxicity. The latter project is in concert with CDER, CBER and CDRH which, hopefully, in the future will lead to a multicenter qualification of such biomarkers in humans. Future projects include collaborations with CDER on, for example, 1) delineating the mechanisms of opioid addiction, 2) assessing the hepatotoxicity potential of oligonucleotide drug impurities and 3) evaluating multiple liver microphysiological platforms for prediction of hepatotoxicity.

Discussion Highlights

- There were no questions for Dr. Schnackenberg

Break from 11:00 am to 11:15 am

Discussion of NCTR Research by SAB members

Dr. Ramos started the discussion by saying he saw an improvement in this meeting as there was a new energy possibly caused by new leadership. However, he continues to be disappointed by the unevenness in the quality of programs across the divisions. They have wrestled with this over his board

tenure. Some of their suggestions have helped but more needs to be done such as impact. There is a need for consistency in how impact is defined across divisions. He believes that publications alone are not sufficient, it should be part of the metrics utilized to track progress of each division. He was intrigued by Dr. Talpos' use of labor hours and all the nuances. Some attention here would be important. He expressed the desire for future presentations to have 1-2 slides devoted to innovation. NCTR is seen as hub of innovation for FDA in many instances in technologies and approaches that permeate and drive agenda for FDA. If divisions could mention innovation, it would help them focus energies on transformative areas but also help guide the ability of the SAB to weigh in and help support and enable those aspirations and investments. Dr. Patterson responded briefly that the metrics to research impact is challenging. There has been a Research Impact Working Group within the FDA for 2 years. It is difficult to standardize an approach. There is a need for peer-reviewed manuscripts, but agency needs are driven by centers which are not after publications. Many times, the stakeholders for NCTR are the product centers but for them it is the American public. CTP has done a great job in this area.

Dr. Cosenza was impressed by the level of enthusiasm and coordination between NCTR centers and divisions compared to the past. This has been a request made by the SAB. This is even more impressive given the pandemic and lack of face-to-face meetings. Dr. Walker noted that she is a new member who listened and learned. What resonates with her was comments by Dr. Ramos. Impact is in the eye of the beholder, and they have the same issue in academia. She asked how projects are being prioritized. If it is requested by other centers, this should be a priority as should something new. She would have liked to have heard why a particular approach was chosen. When is the gold standard approach used (e.g., when it is faster)? What if there are newer techniques out there that may get you there in a more informative way? Were other approaches considered and why were they not chosen?

Dr. Sauer emphasized how great this session has been. The divisions have embraced their guidance around the format of the presentations. He liked it when the rationale for the project was around what a product center needed. At FDA it has to be about applied projects. Impact pieces exist and need to be worked out via discussion and assessment on how to weigh the different pieces.

Dr. Tropsha said others have captured his thoughts. He thought there were great presentations. He agreed that impact and innovation is hard to define as Dr. Patterson mentioned. Data science is emerging more and more and is associated with every research project within NCTR. Can this be captured and used to measure impact and innovation? Collaborations within NCTR and across centers should be captured in metrics. He suggested we work to incorporate research data management into NCTR.

Dr. Lanza also has seen an improvement during his tenure on the Board. In the beginning NCTR focused on peer-reviewed publications only. They do need to put some weight on the impact to centers they are supporting as this is the biggest job. He has been watching AI development (he does this with big companies on imaging). When he looks at AI distribution across FDA, he sees 80% in radiology, some in cardiology with little used elsewhere. NCTR needs to have more interactions with the radiology center which spends most of their time on equipment but is not sure how to make this happen. He suggested NCTR expand the drug types they examine. As a cardiologist he faces issues with newer drugs. They are seeing cardiomyopathies with checkpoint inhibitors, long COVID, etc. He suggests NCTR expands the drugs they are looking at as we move to personalized medicine and the organs affected. He is doing research on proteosome inhibitors which have lots of toxicities. There is room to expand beyond the drugs NCTR is studying now.

Dr. Kaspar thanked all the presenters as he found all talks informative and will not be redundant on comments by other board members. He would encourage ways to assess research impact on goals of FDA. He noticed good coordination between center and NCTR presentations. There is a lot of work to do, lots of areas yet limited funds and personnel. He suggested that we look at priorities and focus on a few of the most important ones that will let NCTR accomplish a lot in that area. Continue to talk about recruitment but maybe look at retention. He asked if NCTR is collecting exit data such as asking if there were issues other than salary. Are center-driven projects leading to frustration as it forces them away from PI-driven projects? He reiterated that there be a focus on retention and recruitment.

Dr. Ganey also felt it was a good meeting as well and touched on personnel issues. Maybe ask people who move to NCTR what their decision was based on. Why did they choose to come to NCTR? Maybe such information can help in recruitment. Does each division need tailored metrics? Issue of prioritization came up in several talks. She remains confused as to how projects are prioritized. If a division starts a project, does this get put on a back burner because it was not initiated by a regulatory center? It was mentioned that funding was reduced and thus it will limit how many projects can be done. This can be an issue in retraining folks.

Dr. Ramos echoed Dr. Ganey's comments and asked to discuss how priorities are set at NCTR. This affects impact and how divisions are reviewed.

Dr. Lanza heard over and over the issue of service agreements for equipment. Why doesn't government have preferred vendor and negotiate government wide agreements? This would free up maintenance money.

Dr. Ganey also wondered if basic equipment could be maintained by an employee vs. individual maintenance contracts. Dr. Lanza said they do that at his institution but a lot of this is proprietary and service agreement costs are very high.

Dr. Patterson said service contract costs are an issue. NCTR does have staff that repair equipment but recent purchases are very high dollar and proprietary so they cannot service this equipment themselves. Overarching service agreements can be an issue as they can be based on prices at headquarters in the DC area versus what they see in Arkansas.

Dr. Gamboa expanded on Dr. Patterson comments. Service contracts are placing an increasing burden on NCTR. For example, it is typical for maintenance contract for a mass spec to be 10% of its cost per year. In the past, they got access to blueprints but now one is buying black boxes and sometimes the parts do not exist in the open market. They may not sell them if they approach the manufacturer. IT can be complex within government to even establish maintenance contracts.

Dr. Talpos commented on the issue of prioritization. What is the data gap for which we can perform an experiment to fill that in? Do science that will answer the question from regulators. Gaps are getting more complex in some areas and may make a bigger impact in other areas. The study of heavy metals is a high priority for CFSAN. The ketamine issue came to NCTR from a reviewer. There is a need to improve communication to identify such data gaps

Dr. Eppihimer cautioned about going to reviewers themselves. When he joined CDRH two years ago, he found that some projects were of concern to one reviewer who wanted to be involved in research instead of a center priority. Dr. Talpos agreed that no project should be started from input from only one stakeholder. Management is responsible for center level priorities. CDRH has made gaps public so all know their priorities.

Dr. Fitzpatrick said CFSAN had this issue, and it was not fair to NCTR if driven by only one CFSAN researcher. There is now a system in place that is working very well. NCTR has been very collaborative and great to work with.

Dr. Tropsha thinks this is an important discussion and clearly FDA itself feels this is an issue. Important to define criteria on how projects are selected and approved. Should look at PI-initiated projects as they are most energized by these. There has been no discussion on how projects are terminated, and this is important as well.

Dr. Foley noted that NCTR's approval process includes sign off by managers in the centers. Projects can be stopped at the concept phase if there is no support at higher levels with little time wasted.

Dr. Ganey asked if anyone wanted to discuss the process for terminating projects. Dr. Foley said many projects run their course on the approved timeline and there is a termination process in the protocol process. In some cases, projects were put on hold because of COVID priorities.

Dr. Eppihimer said it is part of their quality management system. There may be 3 important projects yet there is time to only complete two on time. Tough decisions have to be made.

Dr. Lanza spent a lot of time in industry with yearly prioritization budgets and asked if that happens at FDA. Dr. Patterson said that we can get into more detail in the closed session. In many cases money comes in for particular congressionally mandated work. This gets prioritized.

Dr. Gamboa wanted to bring a nuance to this question. NCTR exists in a regulatory context. By and large NCTR protocols need to have regulatory impact. However, the NCTR staff needs to look at new technologies that may not have a discrete regulatory deliverable now but may enable them to attend to future needs better. NCTR often needs to respond to center emergencies and thus needs capacity to be ready with new tools. Thus, NCTR cannot always identify immediate center need for all projects.

Dr. Ganey thanked the participants, speakers, members of the SAB and the IT folks who enabled the virtual meeting.

The public portion of the meeting concluded at 12:15 pm Eastern