FDA National Center for Toxicological Research

Science Advisory Board Meeting

May 18-19, 2022

These summary minutes for the May 18-19, 2022, virtual meeting of the National Center for Toxicological Research (NCTR) Science Advisory Board were approved on May 26, 2022. 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. Michael Aschner, Ph.D.

Designated Federal Official, NCTR 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/2022-meeting-materials-science-advisory-board-national-center-toxicological-research

May 18, 2022. Meeting began at 9:00 am (Eastern)

The meeting was called to order by the Chair of the Science Advisory Board (SAB), **Michael Aschner, Ph.D**., Professor of Molecular Pharmacology, Neuroscience and Pediatrics, Albert Einstein College of Medicine.

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

1. **Michael Aschner, Ph.D**., Professor of Molecular Pharmacology, Neuroscience and Pediatrics, Department of Molecular Pharmacology, Albert Einstein College of Medicine
2. **Mary Ellen Cosenza, Ph.D., DABT,** President, MEC Regulatory & Toxicology Consulting, LLC
3. **Patricia E. Ganey, Ph.D.,** Professor, Department of Pharmacology and Toxicology Michigan State University
4. **Gregory M. Lanza, M.D., Ph.D.,** Professor of Medicine, Cardiovascular Division, Washington University School of Medicine
5. **Kenneth S. Ramos, M.D., Ph.D.,** Executive Director Texas A&M Institute of Biosciences and Technology, Texas A&M University
6. **John-Michael Sauer, Ph.D.**, Senior Director, Nonclinical Lead, Peptilogics
7. **Alexander Tropsha, Ph.D.,** Professor, Associate Dean for Data and Data Science, UNC Eshelman School of Pharmacy, UNC-Chapel Hill
8. **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

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

1. **Jacqueline O'Shaughnessy, Ph.D.,** Acting Chief Scientist, Office of the Chief Scientist (OCS), Office of the Commissioner (OC)
2. **Karen Elkins, Ph.D.,** Associate Director for Research, Center for Biologics Evaluation and Research (CBER)
3. **Peter Stein, M.D.,** Director, Office of New Drugs, Center for Drug Evaluation and Research (CDER)
4. **Ed Margerrison, Ph.D.,** Director, 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. **Jonathan Kwan, M.S.,** Captain, United States Public Health Service, Team Lead, Research Operations and Advisory Resources Branch, Office of Science, Center for Tobacco Products (CTP)
7. **Regina L. Tan, D.V.M., M.S.,** Director, Office of Research, Center for Veterinary Medicine (CVM) and **Daniel Tadesse, D.V.M., Ph.D.,** Senior Advisor to the Office of Research, CVM
8. **Selen Stromgren**, **Ph.D.,** Associate Director, Office of Research Coordination, Evaluation and Training, Office of Regulatory Science, Office of Regulatory Affairs (ORA)

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

Tucker Patterson, Ph.D., Acting Director
Donna Mendrick, Ph.D., Designated Federal Official and Associate Director of Regulatory Activities
Frederick Beland, Ph.D., Director, Division of Biochemical Toxicology
Steven L. Foley, Ph.D., Acting Director, Division of Microbiology
Robert Heflich, Ph.D., Director, and **Mugimane Manjanatha Ph.D.,** Deputy Director, Division of Genetic and Molecular Toxicology
Richard Beger, Ph.D., Acting Director, Division of Systems Biology
Anil Patri, Ph.D., Director, Nanotechnology Core Facility
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. Aschner (Chair)

- Dr. Aschner opened the meeting and asked SAB members to introduce themselves. He provided an overview of the role of the Science Advisory Board and the purpose of this meeting.

Dr. Mendrick (Designated Federal Official)

- Dr. Mendrick read a statement that assured the attendees that all appropriate ethics regulations were satisfied. No one requested to speak at the public session though we did receive a comment from the Montelukast (Singulair) Side Effects Support and Discussion group as well as individual letters that have been posted on our website.

Dr. Patterson (Acting 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 noted that NCTR has remained productive

throughout the COVID pandemic. Dr. Patterson mentioned some of the COVID-related work being done at NCTR (e.g., wastewater surveillance) and artificial intelligence studies to meet the needs of the regulatory centers. Some of the NCTR work included consults from the centers on drug-induced liver injury (DILI). He highlighted some of the work being done at NCTR in the area of New Alternative Methods (NAMs) including Alzheimer's disease, 3-D bioprinted skin, evaluation of anti-ZIKV therapies, insight into precision medicine of DILI and inhalation toxicology. Dr. Patterson discussed imaging research, studies done with the National Toxicology Program (NTP), work being done within FDA in the Perinatal Health Center of Excellence and ended with an announcement for the upcoming Global Summit on Regulatory Science discussing advances in nanotechnology

Discussion Highlights

- Dr. Aschner was impressed with the new things happening at NCTR. He was concerned that the emphasis on COVID research might have impacted other projects. Dr. Patterson replied that there were supplemental funds earmarked for such research, the pendulum has moved back, and we have a good balance. About 10% of our projects are in the COVID space. Dr. Lanza was impressed with improvements made in AI especially since NCTR is central to FDA and asked if other agencies are interacting with NCTR. Dr. Patterson noted that Dr. Tong's division has a robust collaborative program and much of their work is with other centers. Dr. Lanza thinks NCTR can be a pivot place between centers. Dr. Patterson noted that there is more cross-center interaction than in the past and hypothesized it was due to reliance on virtual meetings. Dr. Tropsha was impressed with the center's progress. He noted that there will be a challenge on relying solely on alternative methods for regulatory decisions and asked, in the transition between NAMS and actual use, how far are we from research to implementation? Dr. Patterson opined that some progress will be made sooner rather than later yet coverage of total body physiology may require using 80 different platforms to replicate a mouse or rat. The challenge is taking small bites and making advances as we move forward. Progress has been made during the pandemic and thinks there will be exponential growth in 5 years or so. Dr. Aschner said that EPA has focused on NAMs as well and suggested that NCTR work with such agencies to ensure there is no duplication of effort.

Subcommittee Review of the Division of Biochemical Toxicology (DBT)

- Dr. Patricia Ganey, Chair of the Subcommittee, discussed the findings of the Subcommittee Review. She noted that their strength is recognized within NCTR, FDA, academics, etc. The publication record is quite good, averaging 50 publications per year. This is a strong division that is doing a good job. With the explosion of alternative approaches, there was a thought that DBT was losing an opportunity to be a leader in providing results from animal studies that could be used in determining the use of new approaches. DBT presented studies in 5 main areas. The first was COVID-19 and the subcommittee felt that DBT was moving too quickly into a short-lived area, but she noted that this was wrong as this year has shown. The second focus area was dermal studies which is an important area. The Subcommittee recommended using a mini-pig instead of rats in one study and was very complementary of their work with 3D bioprinted skin for adsorption studies. The third focus area was in toxicological assessments. They expressed a concern about one in vitro study using multiple cells from the male reproductive tract in that Leydig cells are not available at this time. They felt the study on metformin/glyburide was well planned. A third study was to develop metabolically competent liver cells for use in high-throughput assays. They found the aims were ambitious, but not unreasonable and

recommended DBT consider engaging the pharmaceutical industry. The fourth focus area was in epigenetics which they consider as essential to support translational research. A recurring comment within this area was that the projects, although important, were broad and unfocused, that the novelty was not clear, and some methods were outdated. The last focus area was computational modeling. There was a concern regarding the retirement of Dr. Fisher, a senior scientist, as he had built a program that established effective collaborations with internal and external partners. Dr. John-Michael Sauer, co-chair of the Subcommittee. Dr. Sauer felt that most projects were well done and relevant to the FDA mission and hoped the division will take these recommendations to better the science that is going on.

Dr. Walker made a motion to accept the report as written and this was seconded by Dr. Cosenza. There was unanimous approval by the SAB

Break from 10:13–10:45 am Eastern time

Response to Subcommittee Review

- Dr. Beland, Director of the Division of Biochemical Toxicology (DBT), responded to the Subcommittee Review. He felt that some of their questions might have arisen from his division trying to put too much into the presentations and hoped that the background written material provided to the Subcommittee would help, but apparently questions remained. One high level question was on priorities. DBT interacts with regulatory centers often and while there are DBT-initiated studies, they exist to support the product centers. The Subcommittee had mentioned the personnel lost, mostly due to retirement, and suggested they be replaced with equally experienced individuals. Dr Beland noted that NCTR has had a long tradition of recruiting young scientists who have established very productive research programs. As an example, in the case of the modeling group, there are three staff fellows and three postdocs who work together and have established collaborations with regulatory centers and academics. He feels strongly that NCTR should provide opportunities for existing more junior staff than to always hire highly experienced individuals. There was a recommendation that DBT take a lead in extrapolation between in vitro and in vivo approaches and this division has many such studies ongoing. For example, the Subcommittee was enthusiastic about the 3D bioprinted human skin work. The Subcommittee expressed a concern that the epigenetics effort would benefit from an expert in this area. Dr. Beland said several existing members are well-published in this area and even receive some outside funding. Dr. Beland continued to respond to the individual comments by the Subcommittee.

Discussion Highlights

- Dr. Aschner thanked Dr. Beland for his extensive response. Dr. Walker noted that she only joined the SAB recently and was not part of this evaluation, but felt this was a comprehensive response. As someone experienced in epigenetics, she congratulated them for moving into this area particularly looking at the effects on the liver which she felt was a ripe area for research. She noted that she herself is finding it difficult to keep up with the next generation approaches in this area. All liver cell types are targeting by different things so the ability to tease out their epigenetics response will be transformative. She asked if they could move into multi-omic integration with existing equipment and bioinformatics expertise. Dr. Beland assured her that they can. He brought to the attention of the SAB that there has been difficulty recruiting people

because of constraints of whom can be hired within FDA. Dr. Aschner thanked Dr. Beland for a thorough review and excellent response.

Statement from the Chief Scientist

Jacqueline O'Shaughnessy, Acting Chief Scientist, observed that NCTR's cutting-edge research and contributions can be found just about everywhere in our centers—and they are often central to some of FDA's highest scientific priorities. NCTR holds a unique place as it is the only center that supports toxicological research for all the regulatory centers. Examples presented included NCTR's work on COVID-19, precision medicine, and alternative methods among other areas.

There were no questions.

Dr Aschner mentioned that the SAB has asked that the regulatory Centers present before the NCTR Divisions, and this has happened over the last few years, and will occur in this meeting as well.

FDA Center Perspectives

Dr. Karen Elkins, CBER, provided an overview of the products regulated by CBER, their research goals and their far-reaching scientific expertise. She noted that there are 15 collaborations with NCTR and highlighted three: 1) lipidomic and metabolomic analyses to study neonatal responses as they respond poorly to polysaccharide vaccines, 2) microphysiological systems on placental models and 3) genomics to study off-target effects of CRISPR-based genome editing. NCTR offers needed expertise in lipidomics, developmental toxicology and applying next generation sequencing to toxicology.

Discussion Highlights

- Dr. Lanza expressed an interest in lipidomics. Dr. Tropsha asked about project dynamics and the mechanism of starting a new protocol. Dr. Elkins is relatively new in this role, but mentioned that CBER and NCTR leadership have ongoing discussions. Both Centers send protocols back and forth to find overlapping interests. Dr. Patterson stated that NCTR solicits comments from product centers for NCTR-initiated protocols and equated it to the process undergone by a peer-reviewed manuscript. Dr. Cosenza asked if there was a particular area of interest in reproductive toxicology and Dr. Elkins stated that it is in the area of vaccines since they are unique in that they go into healthy people including pregnant women.

Dr. Ed Margerrison, CDRH, provided an extension from the last SAB meeting held in May 2021. He gave an overview of the Science and Engineering Labs and the recent alignment of their research into specific centers (14 projects in 20 program areas). Many of their researchers also do regulatory reviews and this enables the researchers to understand the regulatory aspect and the reviewers to learn about new technologies. Since devices tend to have gradual changes, there is a slightly different benefit: risk ratio than other centers. Some of their programs are product based (e.g., neurology) while others are more technology based (e.g., machine learning). They have developed regulatory science tools to improve safety and effectiveness of a medical device or emerging technology as most of the innovation comes from small companies. An example included virtual and physical phantoms used in imaging which has been used in three regulatory submissions. Breadth of technology is increasing from other industries such as virtual reality but these companies are not familiar with a regulatory environment like CDRH.

CDRH has published over 100 tools on their website. He has been working with Dr. Patterson on areas that need to be addressed and noted that biocompatibility of medical devices remains an issue and a project will look at the qualification of an in vitro human skin irritation test. They need to increase capacity of building tools and have started discussions with NIH and companies to increase their efforts.

Discussion Highlights

- Dr. Lanza was very interested in AI and said that FDA has the potential to have a tremendous impact because it is being used to remove barriers from medical care being done in rural areas, etc. Dr. Margerrison said that two areas leap to mind. 1) There is a FDA-wide working group for AI. 2) CDRH has a strategic priority for health equality and is looking into how this can be driven into the rural community. Machine learning (ML) will be massive for rural environments and the information flow and its credibility and validation over long distances is critical. This is one of the three critical pillars for CDRH. Dr. Lanza asked if you allow AI to do a multi-step process, are there checkpoints that can move it forward without perfection. How does CDRH look at segmenting the process? Dr. Margerrison said that such close monitoring systems grew out of the alarm situation in every hospital (alarms are sounding so often that caregivers ignore them). They are tied together with decision making processes and these areas are difficult to solve. This also leads into adaptive algorithms. There tends to be bulk updates and CDRH hears about it but when do such changes need to be revalidated? CDRH has established a center of excellence in this AI, and they are taking this area very seriously.

Captain Jonathan Kwan, CTP, presented the Center's goals, regulatory scope, and strategic and research priorities. He presented a graphic on the number of funded projects by research domain. Captain Kwan discussed CTP-NCTR collaborations in the areas of toxicity, addiction, and informatics. Toxicity studies range from pharmacokinetics studies to inhalation studies. Use of an in vitro model of the air-liquid interface is being used to study exposure systems. In the informatics area, there is a collaborative project using natural language processing to search tobacco product marketing applications. Potential areas of future collaborations include inhalation toxicity studies, flavorings, and toxicity of electronic nicotine delivery systems on the air-liquid interface model.

Discussion Highlights

- Dr. Aschner observed that while he understands the move to in vitro and NAMS, asked how they make sure the in vitro data you are collecting can be extrapolated to humans or animals. Captain Kwan said that this is a starting point for future research.

Dr. Peter Stein presented for CDER. CDER is responsible for drugs; it is a large organization and he presented areas from many components, all working with NCTR. They are developing tools or approaches to assess new drug safety and efficacy. There are five research goals : to develop and improve scientific approaches that aid in developing drugs or evaluating post market safety; develop and improve approaches to enhance safety of marketed drugs; improve product manufacturing, testing and surveillance to help ensure the availability of high-quality drugs; develop and improve methods for comparing products to facilitate the development and review of generic drugs and biosimilars; and maintain scientific readiness to address emerging public health threats, enable regulatory integration of emerging technologies and facilitate stakeholder adoption of novel approaches to drug development.

Dr. Stein illustrated collaborations between CDER's Office of Generic Drugs with NCTR (e.g., nitrosamines) and between CDER's Office of Translational Sciences (OTS) and NCTR (e.g., AI models). Areas of greatest include nitrosamines, evaluation of neurotoxicity, etc. There is a need for alternatives to animal models that are predictive of human risk (e.g., MPS). Most of the MPS research is focused on human-derived tissues leaving a data gap in bridging animal data to MPS data. NCTR can conduct bridging studies that will correlate these in vitro technologies with animal studies.

Discussion Highlights

- Dr. Lanza expressed a concern related to cardiotoxicity assessment in vitro since it is not replicating the target organ and some of the clinical toxicity endpoints such as stiffening of the heart. Such models also tend not to consider cardiac protective mechanisms. Dr. Stein agreed but sees a different role for in vitro assays. They are not meant to look at the entire organ system. If there is no adverse signal in animals but is in such an in vitro assay, they might suggest additional preclinical studies or ask to look at signs of cardiac toxicity more in the clinical trial (e.g., imaging). Dr. Lanza commented that what you will find in general is the ability to interrogate is limited. You might be providing insight, but these in vitro systems are looking at the earliest biomarkers of toxicity

Lunch Break from ~1:20–2:00 pm Eastern time

Dr. Mendrick noted that there are no public oral comments so we will start with the next seminars

Dr. Suzanne Fitzpatrick, CFSAN, presented their regulatory mandate (they oversee approximately 90% of the food supply, cosmetics, etc.). She said that they need to find alternatives because it takes too long for animal research once something is on the market. She mentioned ongoing work looking at arsenic toxicity in concert with NCTR using rat and zebrafish models. She thanked NCTR for providing subject matter experts for their work. On the cosmetic side there are multiple projects in collaboration with NCTR. She noted that for many projects they do not have pre-approval authority so need to look at problematic compounds after they are on the market. There are questions of skin penetration of tattoo inks and a model of 3-D bioprinted human skin is being used. The safety of cannabidiol (CBD) in cosmetics is in question and there are joint projects looking at 1) their pharmacokinetics upon dermal exposure, 2) their effect on developmental neurotoxicity and reproductive toxicity, 3) alterations of the neurological immune system, and 4) consequences on male reproduction. There are also studies on the effects of 6:2-fluorotelomer alcohol and brominated vegetable oil. She finished with 1) a mention of a group involved in global harmonization of food safety (ILMERAC) of which CFSAN and NCTR are members and 2) a discussion of the center-wide FDA's Alternative Methods Working Group of which she is chair.

Discussion Highlights

- Dr. Aschner thanked Dr. Fitzpatrick. There were no questions

Drs. Regina Tan and Daniel Tadesse, CVM, discussed the work of their Center. Dr. Tan presented their strategic goals, mission orientation, working style and progress since last year. As part of their strategic goals they want to foster a One CVM culture across organizational boundaries. Their working style coordinates discussions at the Center level so their science is aligned with the regulatory mission. Dr. Tan presented some examples of CVM-NCTR collaborations and showed how easy it is within CVM to see ongoing projects. For every project, there is an impact statement to make sure it is meeting their

regulatory mission. CVM is looking at alternatives, but they will never stop using animals as that is their target population. Dr. Tadesse discussed an example of their use of alternative models, the use of an intestine chip model as an alternative to animal testing to predict the effects of drug residues on the human intestinal microbiome.

Discussion Highlights

- Dr. Aschner thanked them and asked for some research examples between CVM and NCTR and Dr Tan answered.

Dr. Selen Stromgren, ORA, discussed their regulatory mandate and noted that they are not a guidance-setting organization. 80% of their workforce is involved in inspections while the remaining 20% is laboratory based. Their strategic plan deals with many areas such as defensible results, point of entry testing, modernize technology base, etc. There are efforts underway to develop a process to increase compliance with the ORA laboratory manual. The ORA strategic priority plan includes maximizing evidence-based decision making and strengthening scientific accountability.

Discussion Highlights

There were no questions

Presentations from NCTR Research Divisions

Dr. Frederick Beland, Director, Division of Biochemical Toxicology, presented an overview of his division. He discussed the staff, outreach within and outside FDA and the division's mission, goals, strategies, and metrics. Ongoing projects include studies on tattoo pigments, cannabidiols and COVID-19. The first two are in collaboration with CFSAN. Some of the cannabidiol studies are done in concert with CDER. Work on COVID includes wastewater surveillance of SARS-CoV-2. Dr. Beland ended his presentation with division challenges including the inability to hire individuals who have not been in the US for the last several years.

Discussion Highlights

- Dr. Ramos asked how data generated in DBT is provided to the centers. Is it a formal report? Dr. Beland responded that sometimes it is a manuscript, sometimes a report depending on discussions with the centers. He asked about the study on tattoos and whether they are looking at degradation. Dr. Beland responded that they provide data that CFSAN can use. They have not looked at degradation because of insufficient skin size. When they move to mini-pigs they can do it. These compounds are difficult to work with and are very insoluble which is what makes them good for tattooing.

Break from 3:55–4:05 pm Eastern time

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, using artificial intelligence (AI) approaches. He focused on a new program called AI4Tox. This focuses on new AI methods. AI4Tox includes 4 programs: 1. AnimalGAN that uses animal data to generate algorithms in the hope they can predict liver toxicity of new drugs without animal testing, 2. SafetAI initiative was started by CDER to support drug review by building a model using toxicity endpoints important for regulatory review, 3) BERTox, using natural language processing to improve efficiency of document review, and 4) PathologAI to assist the pathological evaluation of organs collected in nonclinical studies. These are for research with the hope in the future it will help FDA's regulatory mission.

Discussion Highlights

- Dr. Lanza asked about accuracy of the models as to the level of false positives and false negatives. Dr. Tong responded that they correlate the in vitro assay with the animal experimental data. Dr. Cosenza was interested in digital pathology as this is a hot topic within contract research organizations (CROs) and other companies have developed products. How does yours compare with what is out there? Dr. Tong stated that their system captures both severity and location. Dr. Tropsha asked if the key differences are between traditional machine learning and other approaches. Have you compared new vs. old methods? Dr Tong responded that new methodologies were derived from conventional machine learning approaches. They do use deep learning and consider this a new method. Dr. Tropsha asked what accuracy is good enough for models to be useful? One needs to dissect sensitivity and specificity. Dr. Tong noted that FDA talks about context of use vs. overall accuracy. They look at adaptive behavior. Does the model become better? They will begin working with CDER's ISTAND process. He agrees that overall accuracy is too simplistic but not time now to discuss. Dr. Aschner asked if there is an effort to share this methodology with other federal agencies. Are EPA/NTP talking to you and taking advantage of this? Dr. Tong said they are collaborating on some projects with these agencies. Dr. Tropsha remarked that AI is rapidly growing, and BERT will remain on top.

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 and CDRH), 2) correcting errors in next generation sequencing to enable the detection of rare events, 3) studying possible mutation methods in an unusual platform and 4) analysis of mutations in highly differentiated in vitro organotypic models. Future projects include development of a biomarker for carcinogenicity with CDER and the application of new and existing genetox endpoints for evaluating genotoxicity of electronic nicotine delivery systems with CTP. Dr. Heflich ended with a discussion of some challenges for his division.

Discussion Highlights

- Dr. Cosenza is interested in their tweaking of the Ames assay for nitrosamine. When do you think the project will be done? Dr. Heflich remarked that they are just discovering this issue so it is open ended. CDER is trying to find out how to address it. Dr. Cosenza remarked that

companies are applying standard techniques, and this might not be correct. One probably needs new approaches.

The meeting adjourned at 5:20 pm Eastern time

May 19, 2022.

Meeting began at 9:00 am Eastern time

Dr. Steven Foley, Acting Director, Division of Microbiology, provided an overview of the staff, mission and outreach. He stressed some areas of their research focus (SARS COV-2-mediated cardiotoxicity, establishment of standardized methods for killing spores, approaches, and challenges in the assessment of xenobiotic-host-microbiome Interaction and the establishment of a database of Salmonella virulence genes). Some examples of ongoing projects included those in collaboration with 1) CVM (the assessment of nanomaterial in sunscreens on the skin microbiome and developing tools to assess antimicrobial resistance), 2) CDRH and CBER (development of in vitro vaginal-tract models), 3) CDER (methods to detect *Burkholderia cepacia* in pharmaceutical products, 4) CFSAN (anerobic methods for detecting microbial contaminants in tattoo and PMU inks) and 5) CDRH (characterization of biofilm formation in antimicrobial-impregnated catheters). Dr. Foley discussed future projects in collaboration with FDA regulatory centers and challenges to the division. The latter included balancing efforts with emerging priorities.

Discussion Highlights

- Dr. Ganey asked if they have looked at vascular tissue. Dr. Foley said that is a good area. Dr. Walker asked if they are profiling microbiome-derived metabolites. Dr. Foley responded that Dr. Khare is doing some of this and a recent hire, Dr. Feye, will be doing this in collaboration with the Division of Systems Biology. Dr. Walker expressed an interest in seeing the microbiome's effect on the immune response and how this applies to toxicity. Dr. Foley said they are looking at this in a number of ways. Dr. Walker said it would be great to have an expert working group on this topic. Dr. Foley replied that they have been involved in the HESI efforts in this area and that Dr. Khare chairs the interagency microbiome working group with NIH and FDA. Dr. Walker ended by saying that the question is not only related to toxicity but also to efficacy.

Dr. John Talpos, Director, Division of Neurotoxicology, discussed his division's staff, outreach, mission, goals, and strategies. He also provided information as to the number of published papers and active projects. As to ongoing projects, Dr. Talpos discussed three: 1) biomarker qualification from bio-imaging, 2) development of a blood-brain barrier in vitro model, and 3) the use of in vitro models to assess the effects of opioids and cannabinoids on development. He also described a project that is using a microphysiological system (MPS) to model Alzheimer's Disease. Highlighted were future projects: 1) assessing acetaminophen-related developmental neurotoxicity in vitro, 2) establishing the impact of damage to barriers of the central nervous system and 3) development of a mini-swine model. Challenges to the division were discussed.

Discussion Highlights

- Dr. Ramos was intrigued by the study of methylphenidate in assessing neurovascular outcomes and asked how are coordinated efforts underway for translational applications. A conundrum

for toxicology is it being animal based yet trying to model human response. Dr. Talpos agreed that this is a challenge. Data shows that the neurovascular is important and folks within CDER says it concerns them, but there are no data showing a regulatory impact. They want NCTR to find it. You cannot just look at a transport protein as there is redundancy. Their initial proof of concept are behavioral studies where a manipulation is done, and they look for changes in behavior or increased cell death. Dr. Ramos remarked that behavior issues lack sensitivity, and one might have significant functional deficits in neuronal function without behavioral signs. A challenge would be to do complementary analysis (omics-based paired with behavioral) or do them in tandem to allow separate interpretation of what you are looking at. He suggest Dr. Talpos consider adding new paradigms such as omics. As to the mini pig model, he agrees with the reason to use them as they are best animal model for emulating the cardiovascular system in humans. Dr. Cosenza asked about the project with CDER to augment nonclinical toxicology assessment by using MRI. Drug development generally uses a one month rat study with histopathology. Is the idea to use MRI or identify biomarkers and where does it within the nonclinical paradigm? Dr. Talpos said that Dr. Liachenko would be best to answer this. He is working on a submission to CDER. He does envision a day when MRI would be used instead of histopathology which does not look at the entire organ. One could use a smaller number of animals and scan every few days and, if an issue is found, directed histopathology could be done in an independent group of animals. Dr. Cosenza was wondering if all CROS would need MRI vs. adding this in a focused study. Dr. Talpos felt it would be easy for CROs to do once they have experience. Dr. Ganey referred to the acetaminophen (APAP) experiment. She asked what the expected concentration of APAP is in the fetal brain after a pregnant woman takes a therapeutic dose. This is important if doing in vitro studies. She asked if they have partnered with DBT in their in silico perinatal model. Dr. Talpos responded that APAP easily crosses the blood brain barrier and is working with DBT. They have a challenge in using a high dose as the onset of hepatotoxicity which causes ammonia release that affects the brain. The project is on hold until they get the pharmacokinetic data to identify the dose. Dr. Aschner questioned if changes in T2 in imaging necessarily meant neurotoxicity as iron deposition can cause such effects. Dr. Talpos said he does not have the personal expertise to answer this question. Dr. Aschner asked why they are emphasizing Alzheimer's disease (AD) instead of trying to standardize their in vitro approach in terms of cell numbers, etc. Dr. Talpos stated that they first started with normal cells, but the interest is to evaluate different AD risk genes. They are working on standardization of the in vitro assay. Dr. Aschner mentioned that CYP 2E1 is sensitive to food intake and one should make sure animals have normal food consumption. On a divisional issue he asked if they have fewer employees than usual and whether these were full time employees. Dr. Talpos said they are down some full time employees and are smaller than usual because he was the Acting Director and, as folks retired, he was hesitant to hire replacements. They will start advertising this summer

Dr. Richard Beger, Acting Director, Division of Systems Biology, described the division staff, organization, outreach, metrics, the division's mission, goals, research interests and strategies. Several ongoing projects were presented and included collaborative work with CDER on the neurotoxicity of montelukast, opioid-induced developmental toxicity, use of a MPS to predict susceptibility and adaptation to DILI, effects of COVID-19 on pregnancy and prenatal/postnatal development, characterizing the viral load and immune cell infiltration in COVID-19 patient autopsy tissues, real-time detection of viruses in body fluids, identifying factors influencing newborn macrophage phenotype and

whether maternal obesity impacts vaccine outcomes, evaluation of drug-induced cardiotoxicity in patient-specific induced pluripotent stem cell (iPSC)-derived cardiomyocytes and the assessment of CAR T-cell toxicities. Future research includes work on cannabinoids, assessment of multisystem inflammatory system associated with SARS-CoV-2 most prevalent in children, use of 3-D similarity machine learning models to predict adverse events from drug-endogenous ligand-target networks, and evaluation of safe violet-blue light on ex vivo stored human plasma and platelets. He finished with COVID-19 projects under development (e.g., Systems-biology evaluation of immune-system variability in COVID-19 patients) and challenges for the division.

Discussion Highlights

- Dr. Tropsha asked about the ligand-target networks and asked if DBB was involved. Dr. Beger replied that is a new approach to a long line of modeling research done within DSB. They are in discussion with CDER as to which drugs to look at and also talking with a bioinformatics expert within the Office of New Drugs. Dr. Tropsha asked about the clinical studies and where samples were being obtained. Dr. Beger responded that samples will be obtained at the University of Arkansas for Medical Sciences and the University of Tennessee Health Science Center in Memphis. Dr. Tropsha asked about the eight open positions and Dr. Beger replied that some are historical and some due to retirement. All are working to identify which areas to move into versus just replacing the person with the same expertise. Once the permanent division director is named, these positions will be filled.

Break from 11:06–11:35 am Eastern time

Discussion of NCTR Research by SAB members

Dr. Aschner thanked the leadership of NCTR and felt there are lots of exciting things ongoing. NCTR is consistently increasing their collaborative research and has excellent scientists and equipment. Research quality is outstanding, and they publish their results in peer-reviewed journals. Much of this work is driven by FDA directives. However, it is not good to re-invent the wheel. NCTR should reach out to other federal agencies to learn about other technologies and bring them into NCTR. It is impossible to be an expert in everything. How do you evaluate metrics for FTEs performance? How many publications per PI do you expect and how do you assess productivity? Such information would be helpful to the SAB. It was disappointing that they heard little about nanotoxicology this time. Does FDA no longer have an interest? We commend you on AI. You are at the forefront in the different kinds of things you are doing and are way ahead of other agencies and institutions. Attrition is a concern, and you are under recruitment issues with foreign nationals. Leadership needs strategies on recruitment. Dr. Lanza also expressed a concern that they heard so little about nanotoxicology since there is so much work in this area elsewhere. He applauded the work being done in AI. As you go forward, try to generate results that you can make into metrics for progress. Compliment you on collaboration within NCTR and CDER and outside academics. Fetal toxicity work is particularly notable as not much is being done in industry and academics. Similarly to Dr. Aschner, Dr. Cosenza has been on the SAB for 4 years and is again impressed with the science, presentations, time, and effort to put together the meeting. She agreed that there is an in increase in collaborations within FDA; interactions within NCTR has improved as well. Recruitment and retention is a continual issue. In the past there was a suggestion to reach out to universities outside regional area to build pipeline. She thinks practically in how the work improves safety of drug development and biologics. There is a balancing concern between urgent issues such as COVID vs. longer term benefit in terms of safety assessment. She encouraged NCTR to focus on

alternative assays for animal work. It is easy to do a one-month animal study so there is a need to keep working on reduction in animal use and asked how this becomes helpful vs. just an add on. In terms of developmental reproductive toxicology, there was an ICH 6 issued last year with a whole section of animal alternatives consideration, but these do not replace animals. Dr. Tropsha stated there was a lot of new science. He is trying to understand how a project is started and terminated and would like to learn about the criteria. Recruitment is a strategic concern as well and would like to hear what it is. There are lots of collaborations but not well articulated on how divisions work together. .For example, all divisions do COVID work but were there cross divisional strategies for collaborations? The output produced by division members was provided in cumulative numbers. Not clear if there are super contributors. Important to develop metrics of individual productivity as well as divisional productivity. Growing important to increase NAMs as regulatory tools. A plan for implementing transition from research to use in regulation would be good to have. Would like to hear about it next time. Dr. Walker commented that this is first time on the SAB, and she has a lot to learn. Recruiting is difficult as she has worked extensively on satellite campuses. There is an opportunity to move into the area of single cell biology in epigenetics and other areas. One can get specific insights and can do multi omics. The Vice Chancellor (Shuk-Mei Ho) at UAMS is an expert in epigenetics. She was impressed with the microbiome work as both a target and a determinant of response. She feels that NCTR has an opportunity, with external collaborators, to make quantum leaps. Dr. Ganey echoed what others said. She also has been on the SAB for 4 years and is always impressed. She has a concern about AI and whether this important utility is driving development. One needs to know in advance how useful it will be. NCTR funds ORISE folks but there was no information on how successful this is to bring people to stay at NCTR. Are there other approaches available to you such as offering perks? All are doing a wonderful job. Dr. Sauer said that NCTR has faced adversity with turnover. The SAB has asked for similarities between presentations in terms of template and this was very good. On the issue of NAMs, many groups (i.e., CDER, industry nonprofits) are doing such work. Does NCTR present an opportunity to show leadership? First time he has heard NCTR using the ISTAND process. These are FDA opportunities to codify NCTR tools; it is hard and takes a long time but important as it bring tools forward. Dr. Ramos was pleased to see progress continues to be made and there has been a maturation of science being portrayed and studies conceptualized. Efforts have been made to highlight interactions across divisions and centers. He provided advice on their regulatory responsibilities and state of the art of their science investment and activities. NCTR needs to balance these equations. Dr. Ramos encouraged NCTR to look for opportunities to grow the portfolio of regulatory science applications and rely on innovation and technology investment as exemplified in some of the talks. He is interested in reports made by NCTR to centers vs manuscripts. Comments provided suggested there isn't a formalized mechanism of deliverables from NCTR. They need to document these; articulation of deliverables and what is delivered is important. They did hear from the divisions about papers, but some clarity should be adjudicated to each project, so you know what they deliver at the end of the project (i.e., papers and/or reports).

Dr. Patterson responded to these comments. Hiring is an issue, yet it depends on expertise we are looking for. It is a sellers' market right now. NCTR had the first ORISE participant in 80s and it has been a great program. Dr. Patterson himself came into NCTR via ORISE. We can retain them if they have the correct expertise. This is a trainee program. We have had good success at retaining them as staff fellows and then FTEs. The government is looking at this issue and trying to convert some of those with valuable expertise with direct hiring. We have been talking about succession planning for years. When you have multiple director positions open, it is difficult to get all on board immediately. Nanotoxicology is still here and going strong. Anil Patri, the head, is on the national nanotoxicology initiative. They have published 3 standards this year. They have received funding for multiple studies. Dr. Patri is looking for

individuals with expertise and has been trying to hire a deputy for 2 years. The work on nanotoxicology has not been presented recently as is not under a division. As to metrics and deliverables, we are looking at it harder. What is significant to the agency and what are clear cut deliverables. Dr. Patterson has been sitting on a metrics working group across FDA. Each regulatory center has different metrics, and they are trying to find some commonality. In our individual performance plan, we all have different projects. Dr. Patterson's plan is tied to specific projects, and this cascades up to the Chief Scientist and the Commissioner. These are high impact research projects. Seen better collaborations across centers and more regular meetings to update on progress. Accountability is important. The ORISE program has been successful, but FDA is moving to a new traineeship program that is flexible in the type of trainee (undergrad to senior scientists). Perks will be better than ORISE. Should be even better than ORISE in recruiting FTEs. Dr. Tong addressed the balance in AI efforts and noted that he is focused on regulatory needs. A lot of his work is reactive from center requests. They are putting models through the ISTAND process. In his division, 50% is research and 50% is responsive.

Dr. Aschner thanked the participants and speakers and the members of the SAB.

The public portion of the meeting concluded at approximately 12:30 pm Eastern time