FDA National Center for Toxicological Research

Science Advisory Board Meeting

May 11-12, 2021

These summary minutes for the May 11-12, 2021 virtual meeting of the National Center for Toxicological Research (NCTR) Science Advisory Board were approved on May 13, 2021.
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/2021-meeting-materials-science-advisory-board-national-center-toxicological-research.

May 11, 2021. 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. **Charles Kaspar, Ph.D.,** Professor & Chair, Department of Bacteriology, University of Wisconsin
5. **Gregory M. Lanza, M.D., Ph.D.,** Professor of Medicine, Cardiovascular Division, Washington University School of Medicine
6. **Kenneth S. Ramos, M.D., Ph.D.,** Executive Director Texas A&M Institute of Biosciences and Technology, Texas A&M University
7. **John-Michael Sauer, Ph.D.**, Program Officer, Biomarker Programs and Executive Director, PSTC, Critical Path Institute
8. **Alexander Tropsha, Ph.D.,** Professor, Associate Dean for Data and Data Science, UNC Eshelman School of Pharmacy, UNC-Chapel Hill

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

1. **RADM Denise Hinton,** Chief Scientist, Office of the Chief Scientist (OCS), Office of the Commissioner (OC)
2. **Karen Elkins, Ph.D.,** Acting 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. **Dana van Bemmel, Ph.D., MPH,** Chief, Research Operations and Advisory Resources Branch, Office of Science, Center for Tobacco Products (CTP)
7. **Regina L. Tan, DVM, MS,** Director, Office of Research, Center for Veterinary Medicine (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:

William Slikker, Jr., Ph.D., Director
Donna Mendrick, Ph.D., Designated Federal Official and Associate Director of Regulatory Activities
Tucker Patterson, Ph.D., Deputy Director of Research
Frederick Beland, Ph.D., Director, Division of Biochemical Toxicology
Steven L. Foley, Ph.D., Deputy Director, Division of Microbiology
Robert Heflich, Ph.D., Director, Division of Genetic and Molecular Toxicology
William Mattes, Ph.D., DABT, 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., Acting Director, Division of Neurotoxicology
Weida Tong, Ph.D., Director, Division of Bioinformatics and Biostatistics

<u>Dr. Aschner (Chair)</u>

- 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 today's meeting. Dr. Aschner noted the loss of Dr. Carl Cerniglia who had been the Director of the Division of Microbiology at NCTR.

<u>Dr. Mendrick (Designated Federal Official)</u>

- Dr. Mendrick read a statement that assured the attendees that all appropriate ethics regulations were satisfied. No one has requested to speak at the public session so we will continue with the agenda. The Humane Society did submit a letter and it can be found on the NCTR Science Advisory Board website with additional materials.

Dr. Aschner commented on the letter by saying that toxicologists are biological scientists.

Dr. Slikker (Director, NCTR)

- Dr. Slikker provided an overview of NCTR with a summary of NCTR staff and research goals. He noted the commitment of NCTR to support the FDA Product Centers. NCTR has many collaborations with outside groups. He highlighted some of the NCTR work that spans divisions such as COVID-19 research and the use of non-animal approaches. He spoke to research being performed in individual Divisions as well. These areas will be addressed in more detail in the presentations given during this meeting by the NCTR Division Directors. He provided a progress update on the new Perinatal Health Center of Excellence (PHCE) and an update on the meetings of the Global Coalition for Regulatory Science Research (GCRSR). The 2021 Global Summit on Regulatory Science virtual meeting will be held on October 4-6.

Discussion Highlights

- Dr. Aschner asked how flexible NCTR has been to adapt to COVID. Dr. Slikker responded that it had a tremendous impact on the laboratory work, yet we also emphasized COVID research. Dr. Ganey asked about a BSL-3 lab. Are you building a new facility or retrofitting an old lab? Dr. Slikker said it takes a quality facility (e.g., air handling, animal rooms) so needs to be a new facility. Looking at Congress for funding. It will take 2-3 years to build and staff the facility.

Subcommittee Review of the Division of Microbiology (DMT)

- Dr. Charles Kaspar discussed the findings of the Subcommittee Review and acknowledged the loss of Dr. Cerniglia. General comments included the finding that the division is productive and collaborates with NCTR divisions and outreach activities at the national and global level have kept research relevant and up to date. A concern was expressed that they may be spreading themselves too thin. He provided overall comments in each topic area. He finished with a summary and future directions. Two highlights were "must build bridges with universities to identify and attract staff" and "the challenge for the Division to identify core strengths and balance with an ever-expanding list of challenges, technologies, and emerging issues." Dr. Cosenza wanted to add her thanks to the Division of Microbiology presenters and the Subcommittee members. Some of the feedback applies to most NCTR divisions, not just Microbiology. She also noted that we need to think of how to improve the pipeline of toxicologists.
  There was unanimous approval of the report.
- Dr. Slikker responded to Dr. Cosenza's comment about training. NCTR is very active training new scientists.

Response to Subcommittee Review

- Dr. Foley thanked the late Dr. Carl Cerniglia who recently passed away. He spoke to the report and thanked the subcommittee for their thorough review. The Division reported on three themes: Food Safety and Virology, Microbiome and Biological Interactions, and Microbial Contaminants Detection. The Subcommittee concluded that ""that the Microbiology Division research focal areas in the program are very relevant and directly applicable to the mission of FDA product safety." Dr. Foley addressed specific comments made by the Subcommittee in their review.

Discussion Highlights

- Dr. Kaspar noted that some recommendations made on personnel were made without a complete background. Dr. Ganey noted that there have been many comments about difficulty hiring scientists and asked for some background. Dr. Slikker responded by saying NCTR needs high quality individuals with particular expertise to work in specific scientific areas. Most of the hiring we do is for postdoctoral scientists with no guarantee they will be hired as full-time employees within the federal government. We do offer competitive opportunities particularly in higher level positions. One difficulty is that we no longer can hire postdocs from out of the country unless they have lived in the U.S. for 3 of the past 5 years, yet that is where most candidates come from. We have hired 26 positions in the last year so do find individuals but it is always challenging. Dr. Tropsha wondered if Dr. Slikker wants to discuss additional training methods that will move us in new directions. Dr. Slikker said that >50% of our projects involve cell culture, non-animal studies, in silico modeling, etc. This movement to new methods has been occurring and we are trying to ascertain their utility to the FDA. We are hiring individuals with backgrounds in these areas (e.g., bioinformatics, cell culture, bioimaging). Dr. Tropsha asked again if something new needs to be done since government keeps asking the FDA to stop animal testing. Dr Slikker noted that the Humane Society letter congratulated FDA for their movement in this area. There is strong support from FDA leaders that you need to verify new approaches before you move them into the regulatory system. Dr. Kaspar asked Dr. Foley if there had been a shift in resources due to the pandemic and what have you learned. Dr. Foley noted that some PIs have moved into COVID research and he learned that if there is a need, people are willing to set aside their main interests into tackling some of these efforts. Dr. Kaspar thanked the division for a job well done.

Morning Break

Statement from the Chief Scientist

RADM Denise Hinton, Chief Scientist, expressed condolences to the NCTR family for the loss of Carl Cerniglia. She complimented NCTR on the work being done in support of FDA and noted the challenges posed by COVID. She highlighted the efforts at the FDA and NCTR specifically in the area of alternative methods. She encouraged all to read the Advancing Alternative Methods report on the FDA alternatives methods website as it describes many research projects. She also discussed the Emerging Sciences and Artificial Intelligence Working Groups run out of NCTR. COVID has shown that we need to worry about animals, humans, etc. RADM Hinton in concert with Dr. Steven Solomon, Director of CVM, chair FDA's One Health platform to improve intra-agency and interagency communication and cooperation in this area. The FDA Science Forum will be held on May 26-27 and is open to the public. All Centers, including NCTR, will present some of their research. Dr. Fauci will be the keynote speaker and she encouraged all to register for the meeting. She thanked the Science Advisory Board for their efforts.

FDA Center Perspectives

Dr. Karen Elkins provided an overview of the products regulated by CBER, their research goals and scientific expertise. She provided some details on their core facilities. Dr. Elkins discussed ongoing CBER-NCTR collaborations: 1. Lipidomics and proteomics analyses in serum and macrophages to address neonatal unresponsiveness to certain vaccines. 2. Development of an in vivo vaginal tract model to

address toxic shock syndrome. 3. Exploration of a microfluidic system to study mouse spermatogenesis. 4. Methods to determine off-target effects of CRISPR-mediated genome engineering and in vitro/in vivo methods for functional evaluation. 5. Examining CAR T cells to identify what contributes to severe inflammatory toxicities. 6. Development of a microphysiological system for evaluating Zika virus sexual transmission countermeasures. She also profiled several new collaborations with NCTR on alternative methods and diagnostics and genomic evaluation.

Discussion Highlights

- Dr. Aschner thanked her for focusing on interactions with NCTR and asked how these projects get started. She responded that sometimes NCTR folks reach out to CBER when they need their expertise and vice versa. Dr. Aschner asked how the physical distances affect these interactions. Dr. Elkins noted that the scientific leadership becomes aware of each other's expertise and individual PIs learn about each other through scientific presentations. Dr. Lanza asked if CBER has addressed a 4-10 year unmet need to realign your expertise that NCTR could address. Dr. Elkins said they have an internal horizon scanning effort at regulatory and research portfolio and constantly seeing if there is a match. They are forward looking and move to gaps while keeping a strong basic research program. Dr. Lanza noted that FDA moved very quickly to address the pandemic and asked how this informed how biologics can move quickly through the approval process. What have we learned from COVID and is it something that NCTR can address? We are actively discussing lessons that have been learned.

Dr. Peter Stein presented for CDER. He provided an overview of CDER research goals and the distribution of projects across these goals. Dr. Stein showed a summary of CDER-NCTR research topics (e.g., targeted organ toxicology in special populations, non-animal models), and provided an overview of preclinical safety monitoring. He showed a case study of a CDER/NCTR collaboration and discussed emerging areas of need. These include alternative models for toxicology testing, asking NCTR to conduct bridging studies to correlate new assays with existing in vivo animal models and/or human clinical outcomes, etc.

Discussion Highlights

- Dr. Cosenza asked if NCTR is helping CDER by using statistics, etc.to reduce the number of animals vs. trying to replace them. Dr. Stein noted that this is an important point as replacing animals is very challenging, but much can be done in reducing the number used. For example, if in vitro assays provide information on toxicity it may lead to the use of a backup compound or can tell us where to focus in terms of organs affected. Dr. Aschner asked if there are regularly scheduled calls to improve communication. Dr. Stein noted that there are opportunities where NCTR staff have come to White Oak to discuss research but not recently of course. They are discussing CDER needs and NCTR capabilities. We can increase such interactions.

Dr. Ed Margerrison, CDRH, spoke to their two areas of big interest; 1) what really happens to implant materials over time, and 2) how do we stimulate upstream innovation. He said that they have very good interactions with NCTR but need to build on this strategically. Ongoing collaborations with NCTR include areas of general toxicity, genotoxicity, etc.. CDRH wants to provide regulatory science tools (i.e., science based approaches to help assess new devices) and showed a CDRH website where one can see current

examples (https://www.fda.gov/medical-devices/science-and-research-medical-devices/catalog-regulatory-science-tools-help-assess-new-medical-devices)

Discussion Highlights

- Dr. Aschner thanked him for his presentation particularly given the COVID pandemic.

There are no public comments so we will reconvene at 2 pm Eastern time with presentations from other Centers.

Break from 1:14 pm to 2:02 pm Eastern time

No comments for the public session so the meeting continued.

Dr. Suzanne Fitzpatrick, CFSAN, discussed their regulatory mandate and how they built upon the original decision tree. The tree will be used to improve screening and prioritization. She presented their program using *C. elegans* to potentially predict human response rapidly as one tool. They worked with NCTR at developmental toxicity of inorganic arsenic in zebrafish and rats. Collaborations in the cosmetic area include tattoo inks. Additional ongoing work with multiple FDA regulatory centers, NCTR and NCATS includes the use of 3D-bioprinted human skin to test permeation. Another CFSAN-NCTR collaboration is a reproductive study in vitro using CBD. Dr. Fitzpatrick discussed the creation of a food toxicology home via a public-private partnership and they are looking at alternative approaches. Dr. Fitzpatrick chairs the FDA's Alternative Methods Working Group that spans the FDA and will strengthen the FDA's commitment to promoting the development and use of new technologies to reduce animal testing. We offer the opportunity for developers to present their mature technology to FDA. More information on the first case study (microphysiological systems), a draft definitions of terms and the publication of a Alternative Report can be found at https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda.

Discussion Highlights

- There was no time for questions, so we moved on.

Dr. Dana van Bemmel, CTP, provided an overview of their regulatory scope and how they evaluate tobacco products. She stressed that science drives decisions. The final rule established 11 warnings for cigarette health warnings. CTP-funded research is having a major impact (e.g., such work has been cited in more than 10,000 publications). Their collaborations with NCTR are in the areas of inhalation, whole smoke exposure in an Air-Liquid Interface (ALI) model and informatics. Several inhalation models have been completed and resulted in publications. Several active studies include pharmacokinetic analysis of nicotine and bridging studies. The ALI model is being used to study chemicals formed when heated. She cited a completed study and its resultant publications and areas of future study. There is an ongoing study using natural language processing to search applications.

Discussion Highlights

- Dr. Aschner asked if CTP regulates e-cigarettes. Dr. van Bemmel answered "yes" and that the center generally refers to them as ENDS but e-cigarettes are essentially the same.

Break from 2:49 to 3:05 pm Eastern time

Dr. Regina Tan, CVM, introduced the Office of Research, its strategic goals, its mission and working style. Their strategic goals include the support of the availability of safe and effective animal drugs, advancement of food safety and safe animal food products, and spread of emerging technologies and innovation. Research must align with CVM needs. Just had a conversation with NCTR on COVID and other areas. CBD is one area.

Discussion Highlights

- Dr. Aschner asked if there are ongoing collaborations and Dr. Tan responded in the affirmative. Dr. Kaspar asked about the salmonella assay she mentioned and wondered if NCTR was involved. They are working with NCTR on a database and other areas.

Dr. Selen Stromgren, ORA demonstrated the size of ORA compared to other areas of FDA and discussed their regulatory mandate. The ORA does not set guidance, it supports agency preventive and enforcement action. The metrics used to study the impact of their research fits into 5 categories: 1) brings visibility to ORA science, 2) increases diversity of their portfolio, 3) increases efficiency/confidence in their methods, 4) adds valuation analytic methods to their toolbox, and 5) used in agency responses. Dr. Stromgren presented several projects. One example is a collaboration with NCTR and CFSAN on the development of machine learning algorithms to assist in automated pattern recognition of organic pollutants in foods and feeds. She outlined 6 collaborations with NCTR and focused on one devoted to exploring an imports development and evaluation tool developed at NCTR that can be used at international mail facilities. Future areas of collaboration include nanoplastics and artificial intelligence.

Discussion Highlights

There were no questions

Presentations from NCTR Research Divisions

Dr. Frederick Beland, Division of Biochemical Toxicology, described his staff, outreach, and mission. He focused on three projects: tattoo pigments, cannabidiol (CBD), and COVID-19. There is a concern that tattoo pigments might cross the placenta and affect the fetus. A mouse model is underway to study this. CBD and hemp-derived ingredients are being added to food and other products. However, there are limited data on the safety of CBD if used chronically. Data in experimental animals suggests adverse effects on the liver and male reproductive system. Studies are underway studying CBD's effects on cultured human and mouse cells. To study the absorption of CBD through skin, a study is examining the pharmacokinetics upon dermal exposure in rats. A rat study is exploring the pharmacokinetics of oral CBD administration and its effect on neurological development. Three projects are addressing COVID-related issues: wastewater surveillance, analysis of anti-SARS-CoV2-antibodies, and development of a life stage-based physiologically based pharmacokinetic model to study potential therapeutics..

Discussion Highlights

- Dr. Aschner asked a general question. NTP is moving away from classical animal studies. Are you involved in validating the assays? Dr. Beland said they do in vitro studies in his division and he thinks it is essential to perform studies to determine if alternative methods can be validated.

Dr. Weida Tong, Division of Bioinformatics and Biostatistics, presented an overview of the division and its outreach, leadership, and mission. They are assisting regulatory centers by improving data capture, developing systems to help pre-market review and providing reviewers with other natural learning-based tools. An example is DeepLabel, a tool that can be applied to drug labeling documents. The division is using in silico approaches to identify combinations of drugs that might be efficacious in COVID as well as the repositioning of existing drugs. They are developing a knowledgebase of opioid agonists and antagonists to help the review process. In the future they will be using more artificial intelligence approaches for a broad array of projects such as deep learning for digital pathology and chemical toxicity.

Discussion Highlights

- Dr. Aschner noted that Dr. Lanza a few years ago stressed that AI should have a much greater role and you have showed that you have implemented a lot of work on behalf of FDA. Dr. Tropsha noted it is an impressive research direction and intrigued by text mining applications. What are the metrics of accuracy you use? Dr. Tong said that text mining tries to address many areas within the FDA. They do not qualify accuracy in each project as some just supply a list. Using labels to predict drug-induced liver injury they get 80% accuracy. Dr. Ramos congratulated him on his presentation and his attention to detail. Regarding the onco panel and your validation for 3 comparisons for tumor vs non tumor - is that a technical or logical (biological) validation? Dr. Tong responded that they asked each sponsor to provide their bioinformatics approach for each onco panel. They asked outside groups to see if their approach could beat the sponsor approach. In that context, this is technical validation. A second question is related to high failure of preclinical models for DILI, how are you informing the knowledgebase for drugs already on the market? Dr. Tong said the knowledgebase is comprised of data based on marketed drugs. Models developed so far cannot affect IND submissions. In several years we might be able to address your question based on post market surveillance data because Smart Template has captured IND data which will used to validate the models developed on post-market data. Dr. Cosenza commented on the great DILI models and noted that until you look at post market data you cannot judge the accuracy. Dr. Ganey asked what are the criteria to decide what goes on the label? Dr. Tong explained this project has not yet started. They will ask AI to read several areas and then ask AI if it would predict it to be a DILI drug and then compare with the human interpretation. They then will ask AI to write a few sentences (text summarization).

Dr. Robert Heflich, Director, Division of Genetic and Molecular Toxicology, provided an overview of their staff, outreach, mission, strategy and metrics for success. He discussed the nitrosamine impurity project being performed in collaboration with CDER. Goals include the development of a potentially predictive Ames test for nitroso compounds and expansion of the CDER database for making read-across predictions. With CBER they are studying adhesion of *Bordetella pertussis* in an in vitro human airway epithelial tissue model (ALI). This work may provide mechanistic insight into the host-pathogen interaction and support this assay as a pre-clinical tool. Future studies using organotypic infections models include a testicular/Zika virus microphysiological model and SARS-CoV-2 drug evaluation using

the ALI model. He also presented an update on his error-corrected (or error-avoidance) next generation sequencing projects.

Discussion Highlights

- Dr. Aschner thanked him for the nice presentation. Dr. Cosenza commented on BioReliance discontinuing their gene tox component and the potential lack of the Big Blue model. Many companies are concerned about this.

The meeting adjourned at 6:01 pm Eastern time

May 12, 2021. Meeting began at 9:02 am

Dr. Aschner welcomed everyone to day 2.

Dr. Steven Foley, Acting Director, Division of Microbiology, described the division staff, scientific expertise, outreach, mission, vision, and metrics. The focus areas include: 1) the evaluation of the impact of antimicrobial agents, food contaminates, etc. on the microbiome, 2) developing methods to detect and characterize microbial contaminants and 3) determining antimicrobial resistance and virulent mechanisms. He described some current and future work in the area of COVID including exploring the role of the nonstructural protein 1 in the virus on modulation of calcium-signaling in transfected cells and discovery of intracellular and extracellular signaling pathways and mechanisms contributing to the complement activation and coagulopathies associated with coronavirus infections. They are assessing microbial contaminants in tattoo inks and permanent makeup products and developing methods to detect *Burkholderia cepacia* complex in pharmaceutical products. They developed an optimized genetic database and algorithms to identify *Salmonella enteria* virulence factors. They are determining whether the microbiome is affected by exposure to compounds such as arsenic, silver, etc. and developing translational approaches. Future projects include modeling COVID-19, and studies to elaborate on the role of plasmid factors in the dissemination of virulence and antimicrobial resistance of bacterial pathogens.

Discussion Highlights

- Dr. Kaspar asked about environmental technology. Is this an active project area and does FDA have oversight? Dr. Foley noted there has been a lot of work historically such as after the gulf oil spill looking at microorganisms and those that can break down oil. Dr. Cerniglia was an expert in this area and we have moved away from this area and moved into tattoo inks, etc. Dr. Kaspar asked about their work on plasmid curing and the use of the toxin-antitoxin systems. Dr. Foley said they are looking at adding a temperature sensitive different plasmid with antitoxin genes, that should allow for minimizing the impact of toxins on bacteria when the plasmids are lost to facilitate curing. This has been a challenging project that is ongoing. Dr. Ganey asked a general question related to outdated labs. Dr. Foley said the Center has been trying to address it by renovating some labs and maybe replace buildings. Dr. Ganey asked if that is sufficient to bring in new technologies. Dr. Foley noted that as space opens up one can judge who fits it best and allows some flexibility.

Dr. John Talpos, Acting Director, Division of Neurotoxicology, spoke about the division staff, its organization, their outreach activities, metrics, and mission. He showed a visual of ongoing projects and highlighted three of them: SARS-CoV-2 and the central nervous system, CBD-related developmental neurotoxicity and immune function, and arsenic-related developmental neurotoxicity. There are a number of ongoing CBD projects in collaboration with regulatory centers. There is a concern that arsenic may cause development toxicity and a mouse study is underway funded by NTP in collaboration with CFSAN. The effect in zebrafish is also under study. Future studies include 1) the effect of heavy metals in combination on the zebrafish, 2) expanding the use of stem cells to study in utero neurotoxicity, 3) quantification of synapses as potential markers of neurotoxicity, and developing a division strategy for neurovascular research.

Discussion Highlights

- Dr. Aschner asked about the doses selected for the metal studies. Dr. Talpos noted that the zebrafish studies will help drive the rodent studies to begin the interaction studies of heavy metals. Dr. Ramos thanked John for the presentation, said he made a great case for the neurovascular unit and in general thinks the premises are on target. However, given the limited resources, asked how he proposes to balance the work. Dr. Talpos noted, for example, that a PI has an interest in TBI which affects high school football players who may be on ADHD medication which is of interest to CDER. Collaborations and support hopefully will lead to resources. Dr. Ramos suggested he write a white paper to generate internal FDA interest. Dr. Ramos also mentioned the issue of density of synapses. The brain is very complex, and they are defaulting to what can be done (e.g., protein framework approach). Overall he appreciated the creative approach being taken. Over the last year he sees more focus and granularity of the questions being asked. Dr. Cosenza asked if stem cell and in vitro models other than zebrafish have been used to look at heavy metals. Dr. Talpos said it will take a lot of work to ascertain if metabolism would occur, etc. She asked if they work in the area of schizophrenia. Dr. Talpos noted that they do not do much work in the area of disease today.

Dr. William Mattes, Director, Division of Systems Biology, spoke about the division staff and its organizational outreach activities, metrics, and mission. Goals include mechanistic studies, evaluating in vitro models for assessment of reproductive, developmental and clinical toxicity, and development of in silico models for predicting toxicities. Examples of current projects include the study of opioids and addiction using animal and in silico approaches, examination of alternative models for cardiotoxicity and hepatoxicity related to precision medicine, and development of advanced tissue imaging technologies. COVID-19 projects include the study of nonclinical safety and efficacy of co-administered investigational therapies and the effects on pregnancy and prenatal/postnatal development. Future projects include identification of clinical biomarkers of cardiotoxicity and study of CBD metabolites in the rat brain. Future COVID-19 projects include the study of long-term effects of the virus on the kidney and improving vaccine effectiveness against variants.

Discussion Highlights

Dr. Ganey liked the results seen with the cardiomyocytes and asked where they are going in the future. Dr. Mattes responded that they have tested 24 of over 100 cells lines and may study another 1200 more and look at the transcripts to identify the underlying differences. They would like to understand the relationship between the phenotype and genotype of the cell lines. On the acetaminophen study Dr.

Ganey asked if they will look at a second drug where the mechanism is less well understood. Dr. Mattes noted they chose acetaminophen because clinically not all respond poorly to acetaminophen so there are many questions still about this drug. Dr. Tropsha thanked Dr. Mattes for a great presentation and noted his work shows the value of in vitro to in vivo human extrapolation. Do you find any systems that do not work? He also noted that their work uses AI and noted they have a huge need. Dr. Mattes said that bringing in computational personnel is problematic. As to whether they have an assay that does not correlate, a PI looked at tyrosine kinase inhibitors to see if their mitochondrial toxicity correlated with their clinical toxicity and found it did not.

Break from 11:15-11:46 pm

Discussion of NCTR Research by SAB members

A discussion of NCTR research was held by the SAB Members. Dr. Aschner thanked Dr. Slikker and the Division Directors with the increase of collaborations across the FDA. He believes the Division Directors have excellent staff, good equipment and publish high quality research in quality journals. They do face an issue with professional recruitment particularly with the restrictions imposed by the federal government. He suggested a task force be formed. He was impressed with internal collaborations and implementing state of the art technologies. Examples include the iPSCs, MALDI work, and artificial intelligence. There is a push for alternative platforms, but he did not get a good idea of whether they validate and provide answers that can be easily extrapolated to humans. He is concerned that some divisions are taking on too much work particularly with the funding environment and suggests they may need to focus on the most pertinent FDA interests. He encouraged improved communication between FDA and the other Centers occur on a regular basis. Dr. Aschner asked the SAB members to provide their impressions of the last few days and, afterwards, Dr. Slikker will respond. Dr. Lanza spoke about the need for artificial intelligence and how NCTR might help regulatory centers in this area, but they need to expand their efforts in this area. He suggested we reach out to consultants instead of trying to recruit FTEs. He did not hear anything about nano and wondered why it was not presented. He hopes he can hear more about it next time. He previously spoke about how NCTR might help the review process with their particular expertise and emphasized this again. Dr. Kaspar was impressed with the progress in a difficult year particularly by the Division of Microbiology and their ability to respond to COVID. There was a repeated theme across the divisions about the balance between near and long term needs. He suggests we value this fluidity rather than fit NCTR into a traditional academic or business model. Does Dr. Slikker have thoughts on how to balance and maintain this fluidity? Dr. Tropsha was impressed with the level of collaboration with NCTR and with the rest of FDA. He spoke to AI and training. This area is focused in Dr. Tong's division, but he sees it expanding into the other divisions. Is it best to embed scientists within each division or centralize it? Dr. Slikker 's presentation mentioned training, which is important, but it is not clear as to whether the Fellows are spread equally among the divisions. Integration of training is important. Dr. Sauer thanked the presenters and thinks the presentation template (discussed at the last session) brought forth needed information. The pharmaceutical side is using alternative methods for compound selection, but can they be used for regulatory decision making? He thinks we should worry about emerging threats and the potentially outdated animal studies used. He thought the response to COVID was excellent. Dr. Ramos saw great improvement in the presentations and the template provided a way to convey the information. He suggests that 1) the achievements for the year need to be highlighted in a more precise way with a limit of 3. This will help the SAB and its stakeholders. 2). When you identify the challenges, it behooves you to present solutions with action items that you will take to address the challenge. The SAB needs to understand how you will address them as this will allow the SAB to be more engaged. 3). There seems

to be inadequate communication across the divisions and NCTR needs to think of ways you can increase communication. Some of the projects presented could have been better if expertise was leveraged across the divisions. Dr. Cosenza highlighted the well run virtual meeting. Staffing issues and scientific education are a repeated concern. She was impressed with the COVID response. Facilities have come up several times during this meeting. Should SAB have time next year to visit the facilities and discussion expansion plans? Communication between NCTR and the other centers seems to be improved. Virtual meetings do provide a good template for communication. She agreed with Dr. Sauer that companies are using MPS in the early phase of drug development vs. regulatory. How do we close that gap? Dr. Ganey thanked all the presenters and the organizers of the meeting. For the presentations by the other centers, it would be important to focus on their interactions with NCTR as the ones that do this well are very helpful in evaluating how NCTR is working with them.

Dr. Slikker responded to these questions as time allowed. He mentioned that NCTR had a science day at White Oak and met with many researchers and leaders from each center. He also mentioned the many working groups and how these venues help exchange information across centers. He said that there has been a lot of progress made in nano and hopes to convey this at the next meeting. Dr. Kaspar mentioned responsiveness and Dr. Slikker mentioned that we need to be responsive to issues that may appear in a short time frame and appreciated his comments. Dr. Slikker addressed comments about the alternative methods work being done and mentioned the Alternative Methods Working Group. He appreciated the input from the SAB and thanked them.

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

The public portion of the meeting concluded at 12:32 pm Eastern time