FDA National Center for Toxicological Research

Science Advisory Board Meeting

November 1-2, 2016

These summary minutes for the November 1-2, 2016 meeting of NCTR Science Advisory Board were approved on _____. I certify that I attended the November 1-2, 2016 meeting of the NCTR Science Advisory Board and that these minutes accurately reflect what transpired.

Donna L. Mendrick, Ph.D.	Martin Philbert, Ph.D.
Designated Federal Official	Chair, NCTR Science Advisory Board

November 1, 2015. Meeting started at approximately 8 am

The meeting was called to order by the Chair of the Science Advisory Board (SAB), **Martin Philbert, Ph.D.,** Dean and Professor of Toxicology, School of Public Health, University of Michigan.

He welcomed the following **Science Advisory Board** (SAB) members:

1. **Susan Felter, Ph.D.,** Research Fellow, Central Product Safety, Procter & Gamble
2. **Diwakar Jain, M.D., FACC, DRCP, FASNC,** Professor of Medicine (Cardiology), Director of Nuclear Cardiology, Westchester Medical Center
3. **Gregory M. Lanza, M.D., Ph.D**., Professor of Medicine, Biomedical Engineering and Biology and Biomedical Sciences; Oliver M. Langenberg Distinguished Professor of the Science and Practice of Medicine, Washington University School of Medicine
4. **Pamela J. Lein, Ph.D.,** Vice Chair, Department of Molecular Biosciences, Professor of Neurotoxicology, UC Davis School of Veterinary Medicine
5. **Suresh Pillai, Ph.D.**, Professor of Microbiology, Texas A&M University
6. **Steven L. Stice, Ph.D.,** Professor, University of Georgia; Georgia Research Alliance Eminent Scholar, Director of the Regenerative Bioscience Center
7. **Katrina Waters, Ph.D.,** Director, Biological Sciences Division, Pacific Northwest National Laboratory

FDA Representatives:

Jose A. Centeno, Ph.D., FRSC, Director, Division of Biology, Chemistry and Materials Science, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health

John S. Graham, Ph.D., MBS, DABT, Director of Research, Center for Veterinary Medicine

Tim McGovern, Ph.D., Associate Director, Pharmacology/Toxicology, Office of Drug Evaluation, Office of New Drugs, Center for Drug Evaluation and Research

David Strauss, M.D., Ph.D., Director, Division of Applied Regulatory Science (Acting), Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research

Dana M. van Bemmel, Ph.D., M.P.H., Assistant Deputy Director for Research, Office of Science, Center for Tobacco Products

Carolyn A. Wilson, Ph.D., Associate Director for Research, Center for Biologics Evaluation and Research

Phil Yeager, Ph.D., DABT, Acting Deputy Office Director for the CTP Office of Science

Other Government Officials:

Alison Harrill, Ph.D., Geneticist, Biomolecular Screening Branch, Division of the National Toxicology Program, National Institute for Environmental Health Sciences

National Center for Toxicological Research (NCTR):

William Slikker, Jr., Ph.D., Director
Dan Acosta, Ph.D., Deputy Director for Research
Donna Mendrick, Ph.D., Designated Federal Official and Associate Director of Regulatory Activities
Frederick Beland, Ph.D., Director, Division of Biochemical Toxicology
Steve Foley, Ph.D., Research Microbiologist, Division of Microbiology
William Mattes, Ph.D., D.A.B.T., Director, Division of Systems Biology
Mugimane Manjanatha, Ph.D., Acting Deputy Director of the Division of Genetic and Molecular Toxicology
Merle Paule, Ph.D., Director, Division of Neurotoxicology
Joshua Xu, Ph.D., Director, Division of Bioinformatics and Biostatistics

Dr. Philbert (Chair)

- Dr. Philbert opened the meeting by welcoming all SAB members, FDA and other government representatives and invited the attendees to introduce themselves.

Dr. Mendrick (Designated Federal Official)

- Dr. Mendrick read a statement that assured the attendees that all appropriate ethics regulations were satisfied.

Dr. Slikker (Director of NCTR)

- Dr. Slikker provided an overview of NCTR with a summary of NCTR staff and research goals. He described how research projects originate and reviewed by the FDA Product Centers and noted that over 50% of NCTR projects are done in conjunction with other FDA Centers. Dr. Slikker spoke of the global coalition and succession planning.

Discussion Highlights

- There was a discussion of the NCTR budget and the balance between legacy and new research proposals. A question was posed by Dr. Stice on the arsenic proposal and how it got prioritized. Dr. Slikker described the recent resurgence in interest in this area and working with CFSAN to develop a number of National Toxicology Program (NTP)-funded protocols. Dr. Reiss inquired about collaborations among institutes, countries, etc. to further knowledge of areas such as biomarkers. Dr. Slikker noted that biomarker qualification takes many years, is usually a group effort and that NCTR works with groups such as HESI on this front.

Subcommittee Review of the Division of Bioinformatics and Biostatistics

- Drs. Waters and Lein led the discussion of the Subcommittee report. They noted that this division plays a great role in implementing emerging sciences into the regulatory review process. An example is the work that has and is being done with MAQC and SEQC. One concern noted is

technology is rapidly evolving as are data types of regulatory review and it may be wise to develop rank metrics to deal with new data types. Predictive toxicology is a major area for the division and they have developed important knowledgebases such as LTKB. The committee felt the miRNA work was underpowered and thought some improvement could be made by improving the depth of their existing knowledgebases while noting these are important contributions to the FDA mission. The biostatistics group focuses most of their energy on the NTP programs and there is a concern that promotion opportunities may be hindered by their focus on service work. The Subcommittee applauded the important collaborations between CDER and this Division and found it to be a very impressive program. They felt the work done in this division to support IT is critical yet it brings additional confusion as to the service vs. research aspect of this division. Overall they felt this division supports the regulatory centers and issued a good review.

- Dr. Philbert asked the SAB for a motion to approve the well-written and thorough report. Dr. Stich made a motion to approach and this was seconded by Dr. Reiss. The vote was unanimous with one abstention (Dr. Lanza had not yet arrived.)

Response to Subcommittee Review

- Dr. Joshua Xu represented the Division of Bioinformatics and Biostatistics and provided an overview of their written response to this review. He thanked the Subcommittee for their thorough review and colleagues from the FDA for their participation. The Subcommittee was tasked with reviewing 5 themes in this division: 1) precision medicine, 2) predictive toxicology, 3) biostatistical approaches and applications, 4) R2R framework and activities and 5) service and support functions. In their report the Subcommittee stated that this division has contributed significantly to the mission of the Agency. However, there was some confusion regarding the boundary between research and support. Dr. Xu felt that this may because the Subcommittee combined service and data analysis support. He stressed that this division works closely with the regulatory centers to ensure that their projects align with the Agency mission. In response to the question concerning the statistical power of the miRNA work, he explained that their goal was to understand whether such biomarkers can be used for mechanistic understanding.

Discussion Highlights

- Topics included how one assesses success in terms of impact on the regulatory mission of the FDA, the balance between building NCTR's bioinformatics infrastructure vs. working on their own analysis projects and prioritization of projects. Dr. Slikker responded to the second question noting that large datasets cannot be easily moved from FDA Center to Center so that NCTR needs its own robust system. Dr. Xu stated that they do look at tools developed outside instead of automatically creating everything themselves. Response to questions regarding priotization of projects led to a discussion of focusing on the FDA mission.

Dr. Frederick Beland (Division of Biochemical Toxicology)

- Dr. Beland presented an overview of his division and its organization. Their focus is to characterize toxicity and carcinogenic nature of compounds of interest to the FDA. They perform varying types of assays including bioassays, epigenetic studies, etc. He presented a few examples including an overview of their work on aloe and furan. Dr. Beland finished with new

initiatives including brominated vegetable oil, inorganic arsenic and an investigation into the mutations seen in animals treated with acrylamide.

Discussion Highlights

- This included a discussion of the susceptibility differences between mice and rats to colon cancer caused by aloin and a philosophical discussion of the usefulness of mutational signatures vs. proteomic/metabolic profiling. The latter may better describe the phenotype but the available human data are mutations. Additional questions were posed on some of the other two new investigations and Dr. Beland welcomed their comments as protocols are still under development.

Dr. Mugimane Manjanatha (Division of Genetic and Molecular Toxicology)

- Dr. Manjanatha represented this division and described the number and type of personnel and some of the collaborations outside FDA including a study of graphene, a nanomaterial. This division also has collaborations with multiple FDA Centers and they play a role in international efforts (e.g., OECD) to validate regulatory tests.

Discussion Highlights

- These included the suggestion that they work in the future in the area of CAR-T immunotherapy. Dr. Manjanatha said it they are anxious to study it as it is a priority area for the FDA Commissioner. In one of his slides he discussed the concept of integrating mutational information with other types of toxicity endpoints and this was discussed further.

Dr. Johann, Jr, (University of Arkansas for Medical Sciences)

- Dr. Johann described his FDA-funded project using liquid biopsies to further precision medicine by targeting molecular vulnerabilities in cancer on an individual basis. He is focusing on lung cancer as it leading cause of death due to cancer in both males and females with a high rate in Arkansas. He will study genetic sequences in blood samples obtained from humans prior to and following drug treatment. He will create a mouse model with the tumor from each individual patient and follow the genetic signatures in mice treated with the same drug given the patient. This effort will require a great deal of bioinformatics collaboration with 5 Arkansas research universities and NCTR.

Discussion Highlights

- These centered on the issues of examining individual patients while extrapolating to the population and whether the fluid under study should be blood or urine (the latter constitution changes frequently during the day).

Dr. Steven Foley (Division of Microbiology)

- Dr. Foley represented this division and provided an overview and how they are enhancing their interactions with FDA Product Centers. They collaborate with all Centers and have a global

outreach as well. Dr. Foley described their research areas and provided three top recent accomplishments. They are working to build capacity for microbiome assessment in toxicology studies performed in conjunction with the National Toxicology Program (NTP) and are collaborating with CBER on studies looking at the immune response following fecal transplant.

Discussion Highlights

- The discussion focused on questions related to the microbiome work (e.g., looking at changes in the microbiome or metabolism of drugs).

Dr. Merle Paule (Division of Neurotoxicology)

- Dr. Paule provided a list of research themes and scientific approaches and collaborations within NCTR and the FDA Regulatory Centers. He described in some detail their work on an *in vitro* blood-brain-barrier model and the effect of stretch on such cells. Dr. Paule provided a progress update on their work discovering biomarkers of neurotoxicity in rats and ended with their research with CDER on an anesthetic agent, sevoflurane.

Discussion Highlights

- There were some questions about methodologies employed and a suggestion that he should add MEA capability.

Dr. William Mattes (Division of Systems Biology)

- Dr. Mattes described the division and collaborations within NCTR, the FDA, other government agencies and universities. He described the goals, strategies and model systems of the division. A brief update on five projects was provided alongside some areas that will be studied in the future.

Discussion Highlights

- It was mentioned that he too might want to employ MEA with their cardiotoxicity work and it was noted that this is being done. The SAB advised them to expand what they are doing in terms of translational work (nonclinical to clinical). The topic of adaptation was raised and Dr. Mattes explained that they are studying this, for example, in a doxorubicin study to separate changes to which the rat can adapt vs. those that progress. Dr. Lanza noted that such work may be useful in the clinic if small changes were supported with systems biology data suggesting the patient would not adapt and that the treatment should be terminated.

The public meeting was adjourned at approximately 5:20 pm

November 2, 2016. Meeting started at approximately 8 am

Dr. Carolyn Wilson (CBER)

Dr. Wilson described the complex products regulated by CBER and presented their 2016 Regulatory Science and Research Goals. She discussed some of the collaborations ongoing with NCTR (e.g.,

PK/PD of vaccine adjuvant and investigation into microbiota impact the immune response to *C. difficule*). Dr. Wilson also described some potential future collaborations between CBER and NCTR.

Discussion Highlights

- These centered on the microbiome work and an acknowledgement that models in animals may not be perfect but is a place to start as we try to understand the microbiota variability and how it impacts infection with *C. difficile*.

Tim McGovern and David Strauss (CDER)

- A description of CDER's pharmacology/toxicology organization was provided as was the regulatory use of pharmacology/toxicology data. Dr. McGovern noted the Office of New Drugs works with NCTR on drugs that are off patent. Dr. Strauss described CDER's Office of Translational Sciences and his Division of Applied Regulatory Science. He profiled some of the projects underway including their work in CiPA.

Discussion Highlights

- A general discussion was held on imaging agents although this was not covered in the presentation above. Other topics including the ongoing work with induced pluripotent stem cells performed at CDER and NCTR, some of which are collaborations.

Dr. Jose Centeno (CDRH)

- Dr. Centeno presented an overview of CDRH's organization and their regulatory mandate. He then focused on the Office of Science and Engineering Laboratories (OSEL) and their role in regulatory science. Their work is aligned with 3 of the 10 regulatory science priorities identified by CDRH. He discussed collaborative work being done with NCTR on nickel and proposed some areas of future interest.

Discussion Highlights

- Topics included a discussion of device sterilization and whether NCTR's work can help identify contamination.

Dr. Dana van Bemmel (CTP)

- Dr. van Bemmel provided an overview of CTP's regulatory mandate and mission. She provided a description of their regulatory science decision making and strategic priorities. Dr. van Bemmel discussed the CTP research portfolio and collaborations with NCTR and other government agencies. She ended with a list of some of the ongoing projects with NCTR.

Discussion Highlights

- It was confirmed by Dr. van Bemmel that CTP does not have their own labs and do their research through collaborative efforts. A brief discussion was held on the regulation of e-cigarettes and how projects with NCTR are selected.

Dr. John Graham (CVM)

- Dr. Graham provided a high level CVM organizational chart and then focused on his Office of Research. He discussed, briefly, the work being done in their Research Divisions. He focused on one study that was done on an arsenic compound approved for use in chickens to improve their growth and how they worked with the manufacturer on their studies. These convinced the manufacturer to voluntarily withdraw this product in February, 2014.

Discussion Highlights

- There were discussions on some of the ongoing CVM-NCTR collaborations and potential areas of future partnerships.

Dr. Sean Linder (ORA)

- Dr. Linder discussed the roles and responsibilities of ORA and their Regulatory Affairs field laboratories (one of these is on the same campus as NCTR). They support the Regulatory Centers in areas of testing such as foods and feeds and nanotechnology. He noted that the latter is an active area of study with NCTR as is the quantification of antibiotics in fecal matter. Dr. Linder proposed some future areas of interest and these include advanced technologies and bioinformatics.

Discussion Highlights

- A brief discussion was held as to funding of ORA.

Dr. Martin opened the meeting for discussion by the SAB members with input by the FDA representatives. Dr. Pillai asked about programs by which folks in the Regulatory Centers visit NCTR and *vice versa* for training. Dr. Slikker noted that there is a program in place for the former while individuals from NCTR visit the Regulatory Centers without necessarily training in mind. Dr. Centeno noted the CFSAN has mechanisms for enhanced training and will explore it with NCTR. Dr. Strauss felt it would be good for scientists from NCTR to work with reviewer's to learn what they do and Dr. Slikker agreed. Dr. Graham noted that Dr. Mendrick is the liaison and has routine contact with the Centers to identify areas of collaboration and Chairs the FDA's Emerging Sciences Working Group. Following up on a question, Dr. Mendrick described this group as being tasked with horizon scanning for the FDA and announced that a recent Federal Registry notice was published to elicit ideas from the public. Dr. Lanza noticed that nanotoxicology is an issue among multiple programs and wondered if NCTR would help. Dr. Graham explained that CVM has collaborations with NCTR in this area and Dr. Wilson stated that NCTR's nanotoxicology expert, Dr. Anil Patri, oversees the FDA-wide nanotoxicology working group. Dr. Felter followed up on a bullet point in the presentation by Dr. Linder regarding a list of expertise in case of emergencies. She asked if outreach is a part of the NCTR's thinking process. Dr. Slikker notes that Dr. Mendrick, the NCTR liaison to the Regulatory Centers, has been invited to join many working groups at FDA and within Centers. A broad discussion was held on metrics of success. All agreed that this is a difficult issue and all are struggling to identify appropriate measures.

The public portion of the meeting concluded