

**FDA National Center for Toxicological Research
Science Advisory Board Meeting
November 6-7, 2014**

November 6, 2014

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

He welcomed the following Board members:

1. **Susan Felter, Ph.D.**, Principal Toxicologist, Central Product Safety, Procter & Gamble
2. **Jay Gandy, Ph.D.**, Professor and Chair, Department of Environmental and Occupational Health, University of Arkansas for Medical Sciences
3. **Diwakar Jain, M.D.**, Professor of Medicine, New York Medical College, Westchester Medical Center
4. **Suresh Pillai, Ph.D.**, Professor of Microbiology, Texas A&M University
5. **David Warheit, Ph.D.**, Senior Research Toxicologist, Acute and Developmental Toxicology, E.I. du Pont de Nemours & Co., Inc.
6. **Katrina Waters, Ph.D.**, Staff Scientist, Computational Biology and Bioinformatics, Pacific Northwest National Laboratory

Other FDA Representatives:

Stephen Ostroff, M.D., Chief Medical Officer (OC)

Todd Bourcier, Ph.D., Center for Drug Evaluation and Research (CDER)

Ronald Brown, Ph.D., Center for Devices and Radiological Health (CDRH)

Carolyn Wilson, Ph.D., Center for Biologics Evaluation and Research (CBER)

Kimberly Benson, Ph.D., and Dana Van Bemmelen, Ph.D., M.P.H., Center for Tobacco Products (CTP)

John Graham, Ph.D., D.A.B.T., Center for Veterinary Medicine (CVM)

Sean Linder, Ph.D., Office of Regulatory Affairs (ORA)

Other Government Officials:

Nigel Walker, Ph.D., D.A.B.T., Deputy Director for Science, Division of the National Toxicology Program, National Institute of Environmental Health Sciences

Presenters from the National Center for Toxicological Research (NCTR) included:

William Slikker, Jr., Ph.D., Director

Dan Acosta, Ph.D., Deputy Director for Research

Donna Mendrick, Ph.D., Designated Federal Official

Carl Cerniglia, Ph.D., Director, Division of Microbiology (DM)

Frederick Beland, Ph.D., Director, Division of Biochemical Toxicology (DBT)

William Mattes, Ph.D., D.A.B.T., Director, Division of Systems Biology (DSB)

Robert H. Heflich, Ph.D., Acting Director, Division of Genetic and Molecular Toxicology (DGMT)
James Chen, Ph.D., Supervisory Mathematical Statistician, Division of Bioinformatics and Biostatistics (DBB)
Merle Paule, Ph.D., Director, Division of Neurotoxicology (DNT)
Julian Leakey, Ph.D., Office of Scientific Coordination
Anil Patri, Ph.D., Director of the NCTR/ORA NanoCore facility
Igor Pogribny, Ph.D., DBT
Xi Yang, Ph.D., D.A.B.T., DSB
James Fuscoe, Ph.D., DSB
Beverly Lyn-Cook, Ph.D., DBT

Dr. Philbert (Chair)

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

Dr. Mendrick (Committee's 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 welcomed the SAB members, Center representatives, and NCTR participants. He noted that this meeting was an opportunity to get advice from the SAB on how to improve the research at NCTR and stressed that the Center representatives also provide valuable input on issues that need to be addressed. The Center Director then gave his State of the Center address. This talk included an overview of NCTR's beginning in 1971 and its mission to conduct scientific research to develop and support innovative tools and the evaluation of approaches that FDA uses to protect and promote individual and public health. The Director emphasized the areas of training and collaborations to improve the global safety net. He explained the process by which research projects are identified and approved and provided examples of collaborative studies (e.g., anesthetics and bisphenol A) between NCTR and the FDA regulatory centers.

Relevant Discussion

- The SAB members suggested some new areas NCTR might want to explore and asked questions about the project approval process.

Dr. Carl Cerniglia (Director of DM)

- Dr. Cerniglia provided a response to the Subcommittee's Site Visit report. The program was judged on the quality of sciences, productivity and integration into the FDA Mission. The site visit presentations were divided into three topics: microbiome and biological interactions, foodborne pathogens, and antimicrobials and pharmaceutical products. The Subcommittee Report agreed that the

Microbiology Division is on track with its mission and vision and was commended for its outreach and educational programs. They were impressed with the quality of science and the effectiveness of Dr. Cerniglia as a leader. The Subcommittee Review suggested a more effective communications plan be implemented with the FDA product centers for better gap analysis and assessment of priorities. Dr. Cerniglia noted that there now are quarterly teleconferences in place between CFSAN, CVM, ORA and NCTR to work toward this goal. He also will work toward improving communications across the FDA to let the regulatory centers know of his Division's capabilities.

Relevant Discussion

- The Subcommittee Co-Chair stated that Dr. Cerniglia's presentation and written response accurately represented the report and found his responses thoughtful and detailed particularly in the areas of collaboration and future areas of interest. Questions were posed regarding the framework in which NCTR operates with Regulatory Centers to identify areas of need and collaboration. The subcommittee identified budgetary restrictions on travel as a possible hindrance on such interactions and suggested he find additional means to interact.

Dr. Acosta (Deputy Director for Research, NCTR)

- He addressed some of the challenges to NCTR and asked for feedback from the SAB. These challenges included how to better explain the relationship of toxicity to improving the health of our citizens and how to develop long term strategic plans to confront changes in technologies in the FDA regulatory mission.

NCTR Division Activities:

Dr. Frederick Beland (Director, Division of Biochemical Toxicology, DBT)

- He described his Division's focus on toxicological assessments, large scale bioassays, mechanistic studies and PBPK modeling. A Subcommittee review of this division was held the day before the this SAB meeting.

Dr. William Mattes (Director, Division of Systems Biology, DSB)

- He defined the mission of this division as addressing FDA strategic priorities in areas such as development of predictive safety models and new technologies, improve methods of safety and toxicity signal detection, and augment methods for detecting foodborne contaminants. He profiled several areas (e.g., discovery of translational biomarkers, understanding the impact of drug-induced mitochondrial toxicity, computational mining). The Division Director then asked for feedback on the current methods and potentially new approaches that could be used.

Relevant Discussion

- SAB members asked for details regarding the types of injury for which this division is exploring biomarkers, its efforts in 3D tissues, high throughput testing and efforts to address personalized medicine.

The meeting adjourned for lunch and open public session.

There was one question from the public during this time. Dr. Alison Harrill (UAMS) commented on the amount of work being done on biomarkers at NCTR and noted that academics are not funded for biomarker qualification even when trying to be translational in nature and move from animals into humans.

Dr. Robert Heflich (Acting Director, Division of Genetic and Molecular Toxicology, DGMT)

- Dr. Heflich spoke about the Division's recent accomplishments, response to FDA chemical-specific needs, and the maintenance and development of regulatory tests. The Director then posed ideas for better integration of genetic toxicology testing into toxicology assessment such as by incorporating new model systems.

Relevant Discussion

- A discussion was held on the assessment of nanoparticles and routes of exposure.

Dr. James Chen (Division of Bioinformatics and Biostatistics, DBB)

- He presented an overview of their accomplishments including the NCTR-driven, consortia effort known as MicroArray Quality Control-3 (aka Sequencing Quality Control, SEQC) project. The presentation ended with the mention of several areas of strategic positioning: next-generation sequencing and work being done with FDA product centers and the challenges of big data.

Relevant Discussion

- Questions were posed on some of the bioinformatics initiatives

Dr. Merle Paule (Director, Division of Neurotoxicology, DNT)

- Dr. Paule provided an update noting the Division's goals are to: 1) develop and qualify quantitative biomarkers of neurotoxicity, 2) identify biological pathways associated with the expression of neurotoxicity, and 3) improve assessment of risk and identify potential therapeutic approaches that prevent neurotoxicity. The Director noted that DNT has made great progress in labeling cells that are dead or dying in unfixed tissue and in cells in culture, which has the potential to change the study of neuropathology.

Dr. Julian Leakey (Office of Scientific Coordination, OSC)

- Dr. Leakey provided an update on the Office and its mission is to support NCTR research programs and protocols in areas such as the NIEHS/NTP studies, veterinary care, nanotechnology through the NCTR/ORA core facility, CTP/NCTR inhalation toxicology, etc. Examples of ongoing studies for the NIEHS/NTP program include bisphenol A, triclosan and arsenic. Additional research being conducted within OSC includes how nanoparticles interact with the immune system and the role of size in liposomal-doxorubicin pharmacokinetics.

Dr. Anil Patri (Director of the NCTR/ORI NanoCore facility, OSC)

- This core facility is dedicated to supporting nanomaterial science conducted at NCTR and throughout the FDA. A listing of current projects include the aforementioned liposomal doxorubicin study, work on graphene being conducted through the AR MOU, and studies being conducted in collaboration with CFSAN, CDER and CDRH. Future directions for this core include increasing collaborations with other FDA centers, other agencies and development of standards.

Relevant Discussion

- The SAB briefly discussed the need for standards in this field and the types of drugs that fit under the designation of “nano.”

Dr. Slikker (NCTR Director)

- The presentation provided an overview and update on the Global Coalition for Science Research (GCRSR). This international group holds yearly global summits to discuss innovative technologies, establish collaborations and partnerships to further translation of basic science to regulatory applications. The most recent conference was held in Montreal Canada with more than 75 participants from 15 countries with a focus on genomics and bioinformatics.

The public portion of the meeting concluded and the closed session began at approximately 4:10 PM.

November 7, 2014

Epigenetics research at NCTR

- The second day started with Drs. Pogribny, Yang, Fuscoe and Lyn-Cook from NCTR discussing research being done on epigenetics and biomarkers of organ toxicity. The presentations ranged from biomarkers of cancer, drug-induced liver injury, how life span changes in the expression of genes may affect drug susceptibility and potential targets of therapeutic evaluation in autoimmune diseases.

Relevant Discussion

- SAB members asked questions as to the usefulness of biomarkers in terms of predicting susceptibility and their rate of change.

Dr. Stephen Ostroff (FDA Chief Scientist)

- Dr. Ostroff described his office that incorporates NCTR, Office of Women’s Health, Office of Counterterrorism and Emerging Threats among others. He also discussed the Centers of Excellence in Regulatory Science and Innovation and the Broad Agency Announcement Program. He stated that better communication between NCTR and the Regulatory Centers is important.

Dr. Nigel Walker (National Toxicology Program, NTP)

- Dr. Walker explained that NTP is an interagency program housed at the National Institute of Environmental Health Sciences (NIEHS). He discussed the Tox21 interagency initiative and presented a historical perspective of the NIEHS-NCTR agreement. He finished with a list of needs (e.g., improve interactions between academic, government and regulatory scientists) and opportunities in the area of toxicology (e.g., improved science base for extrapolation between *in vitro* and *in vivo*).

Dr. Todd Bourcier (CDER)

- Dr. Bourcier presented an overview of the pharmacology and toxicology data required of new drugs and discussed some areas of potential collaboration between CDER and NCTR (e.g., in the area of *in vitro* developmental assays).

Dr. Ronald Brown (CDRH)

- Dr. Brown discussed some of their work in the area of biomarkers and proposed potential areas of collaboration such as the identification of miRNAs for specific endpoints of interest to CDRH. Also mentioned was a need to improve the extrapolation from various routes of exposure.

Relevant Discussion

- A SAB member described the clinical interest in biomarkers of cardiotoxicity

Dr. Carolyn Wilson (CBER)

- Dr. Wilson presented the regulatory mission of her center and the role of research. She identified three areas of potential collaboration such as using bioimaging for the trafficking and functional analysis of neural stem cells.

Dr. Dana van Bommel (CTP)

- Dr. van Bommel described their mission and provided some examples of funded research projects that feature epigenetic biomarker goals. She ended with a slide showing the 10 interest areas published by CTP for which both federal agencies and extramural groups can apply for funding.

Dr. John Graham (CVM)

- Dr. Graham discussed issues surrounding the use and acceptance of biomarkers. He noted the use of a swine inflammation model to identify biomarkers of inflammation. Dr. Graham noted the development of new relationships between CVM and NCTR to identify areas of mutual interest.

Dr. Sean Linder (ORA)

- Dr. Linder described the ongoing ORA-NCTR collaborations in the area of nanotoxicity and provided examples of how techniques developed at ORA in areas outside of nanotoxicity can help NCTR and *vice versa*.

Relevant Discussion

- Again members of the SAB asked the Center Representatives about the process of identifying needs and understanding how NCTR might assist them

The Chair thanked the Center representatives and the NCTR Division Directors for their participation.

The public portion of the meeting concluded and the closed session began at approximately 12:15 PM.