

FDA National Center for Toxicological Research

Science Advisory Board Meeting

November 3-4, 2015

Meeting attendees:

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 Board members:

1. **Susan Felter, Ph.D.**, Research Fellow, 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., FACC, DRCP, FASNC**, Professor of Medicine (Cardiology), Director of Nuclear Cardiology, Westchester Medical Center
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. **David Warheit, Ph.D.**, Senior Research Toxicologist, Acute and Developmental Toxicology, E.I. du Pont de Nemours & Co., Inc.
7. **Katrina Waters, Ph.D.**, Director, Biological Sciences Division, Pacific Northwest National Laboratory

FDA Representatives:

Robert M. Califf, M.D., Deputy Commissioner for Medical Products and Tobacco, Office of the Commissioner

Luciana L. Borio, M.D., Acting Chief Scientist, Office of the Commissioner

Cathy L. Backinger, Ph.D., M.P.H., Deputy Director for Research, Office of Science, Center for Tobacco Products

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

Paul E. Norris, DVM, Director, Office of Regulatory Science, Office of Regulatory Affairs

Lilliam A. Rosario, Ph.D., Director, Office of Computational Science, Office of Translational Sciences, Center for Drug Evaluation and Research

Dana M. van Bemmelen, 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

Other Government Officials:

John R. Bucher, Ph.D., Associate Director, National Toxicology Program; Director, National Toxicology Program Division

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

Frederick Beland, Ph.D., Director, Division of Biochemical Toxicology

Carl Cerniglia, Ph.D., Director, Division of Microbiology

Robert H. Heflich, Ph.D., Director, Division of Genetic and Molecular Toxicology

Anil Patri, Ph.D., Director of the NCTR/ORA Nanocore facility

Merle Paule, Ph.D., Director, Division of Neurotoxicology

Weida Tong, Ph.D., Director, Division of Bioinformatics and Biostatistics

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

November 3, 2015

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 a state of the NCTR including their goals, how they work with the FDA regulatory centers and showed a pie chart of the breakdown of the 2015 projects with FDA regulatory center collaborators. He highlighted 3 accomplishments in 2015; briefly they were 1) building scientific partnerships with FDA and with external collaborators, 2) expanding the Global Coalition of Regulatory Science Research, and 3) enhancing NCTR organizational and facilities activities to optimize cutting-edge science and collaborative partnerships. Dr. Slikker asked for the SAB Board's input on further alignment of FDA research needs and available resources at NCTR. He also asked them for horizon scanning to prepare NCTR with ideas of disruptive sciences, provide advice on scientific partnerships and global interactions. Several board members asked about the ability of NCTR to work with industry and Dr. Slikker explained the options available to FDA.

Discussion Highlights

- Dr. Philbert asked the FDA regulatory centers why they like to work with NCTR. Responses included the fact that NCTR scientists are hardworking, it is easy to share confidential information with them, the give and take that can occur within an agency and how easy it is to pivot as a project moves forward, how it can move research from lab to the field faster, and the fact that NCTR has unique capabilities. Dr. Lein asked if NCTR works on biologics and obesogens

and Dr. Slikker responded in the affirmative to both. Dr. Warheit noted that good progress has been made on the Nanocore.

Dr. Frederick Beland (Director of DBT)

- Dr. Beland presented an overview of his division, highlighted some accomplishments and described how they have strengthened computational toxicology within the last 5 years. This division collaborates with all NCTR divisions, each of the FDA regulatory centers, other government agencies, universities, etc.
- Dr. Beland went on to address the SAB subcommittee review of his division that occurred in November 2014. For the review he presented four themes: 1) dietary contaminants and supplements, 2) phototoxicity and skin carcinogenesis, 3) epigenetics and *in vitro* methods development, and 4) pharmacokinetic modeling. He presented examples of where he has taken the advice of the subcommittee in protocols and approaches. Dr. Beland highlighted the fact that the National Toxicology Program (NTP) studies completed within his division and the NCTR in general are focused on compounds suggested by FDA centers and that these same centers are heavily involved in the study design and receiving routine updates of study progress.

Discussion Highlights

- Dr. Gandy, co-chair of the subcommittee review team, felt that the response to the subcommittee report was excellent. There were discussions around the potential phototoxicity of triclosan, the need to develop a high throughput screen for compounds that cause epigenetic changes, and on their nanosilver studies. Dr. Felter offered that the committee could comment on protocols early in development.

Dr. Robert Califf (Deputy Commissioner for Medical Products and Tobacco) spoke to the meeting remotely

- Dr. Califf discussed some of the regulatory science needs of the FDA including integration of systems biology with big data obtained from the clinic and the need to link biomarkers with clinical endpoints. He noted the importance of human phenotyping such as at the maternal-fetal pair that changes daily and is not amenable to studies done with other phenotypes. He suggested this get more emphasis at NCTR. Dr. Califf discussed the need to optimize FDA interactions with the global regulatory world and scientists and noted that NCTR is involved in research at the global level.

Dr. Luciana Borio (Acting Chief Scientist)

- Dr. Borio noted the need to attract, train and retain the best at FDA as it is the backbone of the organization. She discussed the Center of Excellence in Regulatory Science and Innovation (CERSI) program and how they can help the FDA move forward in areas such as the precision medicine initiative. She expressed gratitude for the FDA's Science Board subcommittee report (Science Moving Forward) and explained that many of the activities in this report are already in progress.

The meeting was adjourned at approximately 4:30 pm

November 4, 2015

Dr. Lilliam Rosario (CDER)

- Dr. Rosario spoke of the need to provide services that directly impact the reviewers. She highlighted some collaborations with NCTR on Research-to-Review and Return (R2R). Items include the Liver Toxicity Knowledge Base (LTKB) and the FDALabel drug labeling database.

Dr. Jose Centeno (CDRH)

- Dr. Centeno provided an overview of CDRH, its mission and that of the Office of Science and Engineering Laboratories (OSEL). CDRH is working with NCTR on two of CDRH's FY16 regulatory science priorities: computational modeling and modernizing biocompatibility/biological risk evaluation of risk materials.

Dr. Carolyn Wilson (CBER)

- Dr. Wilson described their regulatory mandate and two collaborations with NCTR in the area of *Clostridium difficile* infection and next generation sequencing. She also noted two areas of potential future collaboration.

Dr. Cathy Backinger (CTP)

- Dr. Backinger described their regulatory authority and strategic priorities. CTP is working with NCTR on multiple projects in the categories of informing products standards, informing comprehensive nicotine policy, and pre- & post-marketing review.

Dr. John Graham (CVM)

- Dr. Graham provided CVM's mission and that of the Office of Research and spoke to several areas of research including the Veterinary Laboratory Investigation and Response Network and the National Antimicrobial Resistance Monitoring System (NARMS). Future research involving NCTR may include research on stem cells use for veterinary purposes, additional work on nanoparticles (he noted the excellent facility at NCTR), and PBPK modeling.

Dr. Paul Norris (ORA)

- Dr. Norris described their surveillance work, the existing ORA laboratory locations and the ongoing reorganization. He listed the extensive areas of testing and external collaborations.

Dr. Weida Tong (Director, Division of Bioinformatics and Biostatistics, NCTR)

- Dr. Tong described the work done within the division that combines research and support of other centers and NTP projects. He described collaborations with other NCTR divisions and FDA centers and their global outreach. He discussed the division's priorities and presented several top accomplishments within the last year or so. He also described some future work such as the second iteration of the Sequencing Quality Control (SEQC) effort.

Discussion Highlights

- SAB members discussed the changing nature of whole genome sequencing, the challenges in data interpretation, and the use of animal models to predict population-based and individual risk. Dr. Pillai noted that NCTR should be working to harmonize whole genome sequencing analysis and Dr. Wilson (CBER) responded that there is an internal FDA working group and there may be a need to use different approaches in various Centers but there can be a harmonization in some aspects.

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

- Dr. Heflich provided his division's mission, its goals and strategy. He provided information on several areas in which they are involved in the development and validation of regulatory tests. He ended with his strategy for the future.

Discussion Highlights

- The discussion included how one might define thresholds and add quantitative, dose-response data to the study of gene mutations.

Dr. Patri (Director, Nanocore, NCTR)

- Dr. Patri provided the mission of the Nanocore and his strategies. Collaborators inside NCTR, other areas of the FDA, and government agencies were listed as was global outreach. He provided 5 accomplishments that were completed within the last year or so and listed 6 current projects as examples.

Discussion Highlights

- A discussion was held on the sunscreen project, some suggestions as to additions to the study examining doxorubicin liposomes, and the development of standards.

There were no comments during the open public session

Dr. Cerniglia (Director, Division of Microbiology, NCTR)

- Dr. Cerniglia described his divisions' mission and vision and presented his research themes. An overview of the collaborations and outreach was provided as well as several highlighted accomplishments. He provided insights into the research on the horizon and overall strategy.

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

- Dr. Mattes provided information on the division's collaborations within NCTR, FDA regulatory centers, other government agencies and universities. The division's mission, goals and strategies were explained and 6 accomplishments within approximately the last year were highlighted. Current projects were illustrated and future directions discussed.

Discussion Highlights

- A discussion of several projects ensued. Dr. Philbert noted that we need to define adaptive vs. phenotypic changes and move away from single endpoints. There was a longer discussion of the proposed study of tyrosine kinase inhibitors and how these might best be approached.

Dr. Paule (Director, Division of Neurotoxicology, NCTR)

- Dr. Paule presented his division's mission, research themes and model systems used. He highlighted 3 accomplishments within the last year or so as well as outreach to other NCTR divisions and FDA centers. He described global outreach efforts and future directions.

Discussion Highlights

- A discussion ensued regarding biomarkers, and the safety assessment strategies for ketamine and gadolinium.

The Chair thanked all attendees for their participation.

The public portion of the meeting concluded and the closed session began