FDA National Center for Toxicological Research

Science Advisory Board Meeting

March 19-20, 2019

These summary minutes for the March 19-20, 2019 meeting of the National Center for Toxicological Research (NCTR) Science Advisory Board were approved on March 38, 2019. I certify that I attended the March 19-20, 2019 meeting of the NCTR Science Advisory Board and that these minutes accurately reflect what transpired.

____/s/_____ ____/s/_____

Donna L. Mendrick, Ph.D. Pamela Lein, Ph.D.

Designated Federal Official, NCTR Chair, NCTR Science Advisory Board

A verbatim transcript will be available and posted at https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/ToxicologicalResearch/ucm624908.htm.

March 19, 2019. Meeting started at 8:01 am

The meeting was called to order by the Chair of the Science Advisory Board (SAB), **Pamela Lein, Ph.D.,** Vice Chair, Department of Molecular Biosciences and Professor of Neurotoxicology, UC Davis School of Veterinary Medicine.

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

1. **Michael Aschner, Ph.D.**, Professor of Molecular Pharmacology, Neuroscience and Pediatrics, Department of Molecular Pharmacology, Albert Einstein College of Medicine
2. **Susan Felter, Ph.D.,** Research Fellow, Central Product Safety, Procter & Gamble
3. **Charles Kaspar, Ph.D.,** Professor & Chair, Department of Bacteriology, University of Wisconsin
4. **Pamela J. Lein, Ph.D.,** Vice Chair, Department of Molecular Biosciences, Professor of Neurotoxicology, UC Davis School of Veterinary Medicine
5. **Steven L. Stice, Ph.D.,** Professor, University of Georgia; Georgia Research Alliance Eminent Scholar, Director of the Regenerative Bioscience Center

FDA Representatives from Centers other than NCTR:

1. **Mary E. Allen, MS., Ph.D.,** Deputy Office Director, Office of Research, Center for Veterinary Medicine (CVM)
2. **Jason Aungst, Ph.D.,** Supervisory Consumer Safety Officer, Center for Food and Safety and Applied Nutrition (CFSAN)
3. **Susan M. Chemerynski, Sc.D., MPH**, Toxicology Branch Chief, Division of Nonclinical Science, Office of Science, Center for Tobacco Products (CTP)
4. **RADM Denise Hinton,** Chief Scientist, Office of the Commissioner (OC)
5. **Jonathan Kwan, MS,** Program Analyst, Office of Science, CTP
6. **Ed Margerrison, Ph.D.,** Director, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health (CDRH) via telecon

7. **Juan Ruiz, Ph.D.**, **MBA,** Deputy Director for Science, Office of Translational Sciences, Center for Drug Evaluation and Research (CDER)
8. **Hans Rosenfeldt, Ph.D.,** Deputy Director, Division of Nonclinical Science, Office of Science, CTP
9. **Selen Stromgren, Ph.D**., Associate Director for Research Coordination and Evaluation, Office of Regulatory Affairs (ORA) via telecon
10. **Dana van Bemmel, Ph.D., MPH,** Branch Chief, Office of Science, Center for Tobacco Products (CTP)
11. **Carolyn A. Wilson, Ph.D.,** Associate Director for Research, Center for Biologics Evaluation and Research (CBER)
12. **Tong Zhou, Ph.D., DABT**, Supervisory Toxicologist/Leader, Toxicology Team. Office of New Animal Drug Evaluation, CVM

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
Frederick Beland, Ph.D., Director of the Division of Biochemical Toxicology
Carl Cerniglia, Ph.D., Director of the Division of Microbiology
Sherry Ferguson, Ph.D., Director, Division of Neurotoxicology
Robert Heflich, Ph.D., Director of the Division of Genetic and Molecular Toxicology
William Mattes, Ph.D., DABT, Director, Division of Systems Biology
Anil Patri, Ph.D., Director of the Nanotechnology Core Facility
Laura Schnackenberg, Ph.D., Research Chemist, Division of Systems Biology
Weida Tong, Ph.D., Director, Division of Bioinformatics and Biostatistics

Dr. Lein (Chair)

- Dr. Lein 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. NCTR's main goal is to generate data to support the FDA mission. He provided three top accomplishments in 2017/2018 and illustrated how the research at NCTR supports the FDA Product Centers. He touched on succession planning and provided details of the new Perinatal Health Center of Excellence (PHCE).

Discussion Highlights

- The discussion focused on the future of NCTR personnel, budget and computational and *in vitro* approaches. The shift from animal to non-animal approaches has been happening over many

years. The number of personnel has remained relatively stable but the NCTR budget has not been increasing like that of the rest of the FDA.

Subcommittee Review of Analytics

- Drs. Stice and Aschner were chair and co-chair, respectively, of the Subcommittee. Dr. Stice provided a summary of the report that reviewed the analytics area (nanocore to bioimaging to bioanalytical imaging, to modeling). It was noted that these are valuable resources to FDA and the Subcommittee was very impressed by the leadership, excellence in science and accomplishments particularly given the resources available. They strongly recommend this be supported and mentioned that the future is in collaborations and response to FDA needs. The Director should continually assess the areas of research as scientific needs change as they need to incorporate emerging areas as they develop.
- In some areas there is insufficient staff, so it was mentioned that there may be opportunities for cross-training of individuals, which will also lead to sharing knowledge.
- It was evident from the presentations that there are cutting edge technology capabilities and equipment. Nano is an excellent program with world class leadership and this core has equipment and knowledge for current FDA review horizon. They found the imaging platforms to be appropriate while the discovery and qualifications of new biomarkers for neurotoxicology to be challenging. The MRI work is outstanding, the results are excellent, and they hope more will come from this staff in these areas. Maintenance agreements are expensive but trying to be innovative in using resources is important. Limited term employees such as postdocs can be problematic because their rapid overturn equates to loss of corporate memory and disruption when they leave. They hope these areas get more long-term staff. Good productivity in material analysis but it is very project specific. The potential exists to create a broader and higher impact center with new software and personnel.
- The Subcommittee was asked for input on what is on the horizon that NCTR should explore. They want to be cautious because of the thin staff but there are some trends outlined in the report. Nano science (vaccine development to exosomes, etc.). could be explored in biologics area. Labeling of nano particles important to better understanding of biodistribution, safety clearance, resident time for immunotherapy, etc. The whole range of analytics is an area of high need for all of FDA and they suggest NCTR continues this area of focus.
- Dr. Aschner noted that NCTR needs to be focused and in those areas, there is a need for additional personnel. Other centers are doing similar things so focus on areas with added value and this is done through cross fertilization between NCTR and other centers.
- There was unanimous approval of the report.

Response to Subcommittee Review

- Dr. Schnackenberg spoke to the report and thanked the subcommittee for their careful review. It is difficult to train people in the diverse areas but identified some ways it might be possible. Adding to existing staff would be optimal and they have ongoing collaborations with multiple groups. Specific areas addressed by her were imaging assessment, image analytics, etc. Cross center collaboration is encouraged as this will help develop analysis tools. The Subcommittee asked that efforts be made to translate MR imaging biomarkers from animals to humans. Dr. Liachenko is preparing a letter of intent to the Biomarker Qualification Program at CDER.

- The Subcommittee said there is a challenge to increase the impact of imaging at NCTR and noted a need for image co-registration capabilities between platforms. Dr. Schnackenberg agreed. There is a need to increase other capabilities at NCTR and she listed them (e.g., increase external bandwidth).
- Dr. Patri addressed the nanotechnology core facility review by the Subcommittee and thanked them for their comments. He will pursue cross-training opportunities in image analysis and will collaborate with the Advanced Biomedical Computing Center at Frederik National Lab for Cancer Research. He is investing in standards as this can have a significant impact.
- Dr. Patri noted that he can buy software but needs experts in analysis and showed a slide of drug product submissions. Many are soft material vs. heavy metals. So, there are more submissions and they are more complex. For example, projects are centered around liposomes and slight changes in surfaces change their biodistribution, etc. as most are iv administered.
- The nanocore is working in areas of emerging needs (e.g., ligand targeting) and will develop a complement activation assay as a guide and/or standard test method.

Discussion Highlights

- It was suggested that the imaging facility be made a core and combine PET and MRI in studies. The kind of findings NCTR can put together is a strength and that they just need to get the software. Many groups are using non-commercial software.
- There is some ongoing co-registration work correlating MRI to other endpoints such as histological images.
- The Nano Task Force started in 2006 out of the Office of Chief Scientist and representatives are nominated by each Center. Their Charter is to look at FDA challenges. They provide grants within FDA and coordinate across the agency on nano. CDRH also has a nano core facility. One hundred and twenty reviewers have been trained. An exchange of personnel for a month or so would be a way to cross-fertilize.
- Several of the Global Summit meetings have been nano-based. Dr. Patri recently got high praise from the US government for his outreach to India. They have taken on a guidance like that used in the US.

<u>Dr. Frederick Beland (Division of Biochemical Toxicology)</u>

- An overview of this Division's staff, outreach and mission was provided. Brief summaries of historical studies and data gaps were provided. These data are used by regulatory authorities (e.g., Health Canada used the furan study). A proposed inorganic arsenic bioassay was presented to address key data gaps. Pegylated (PEG) biopharmaceuticals are being used for chronic administration and there is a concern of PEG deposition in tissues and its long-term effects. Proposed studies were discussed, and they will begin with toxicokinetic profile and biodistribution. Nattokinase and lumbrokinase are currently being studied in rats. They are taken as dietary supplements because of claims of positive effects on cardiovascular health. There is a concern that they may increase the risk of bleeding when used individually or with aspirin. A study is underway, and they found that both lumbrokinase and nattokinase reduce the anti-platelet aggregation effect of low dose aspirin in rats.
- A 4th project is looking at Oseltamivir pharmacokinetics. This drug is used to treat influenza although the dose required for pregnant women is not known. The study is looking at pharmacokinetics of the drug.

Discussion Highlights

- Questions were asked about incorporation of newer technologies such as toxicogenomics in target organs to build a better understanding of genetic level changes as they correlate to apical changes such as histology. Some of these questions are being addressed via cell culture and Dr. Cerniglia is looking at gut microbiome changes. A discussion was held as to doses and whether we look at low levels of exposure. The arsenic study is using a low dose.
- It was asked it there is a plan to study neurodevelopment upon exposure to CBD. There is a lot of interest in this class of compound and NCTR has a long history with working with marijuana smoke and THC (20 years ago). Still many open questions.

Dr. Weida Tong (Division of Bioinformatics and Biostatistics)

- Dr. Tong provided an overview of his Division and some of their collaborations with other FDA Centers. An example is work being done for CDER on supporting the DASH (Data Analysis Search Host) tool which tracks approval of applications in CDER. His division was asked to upgrade the tool and create a new front end, provide visualization capability, etc. Dr. Tong presented 2 past accomplishments, the MicroArray Quality Control (MAQC) consortium and the building and use of the Liver Toxicology Knowledge Base (LTKB). As an example of a current project is working they are doing on the challenges of applying toxicogenomics in risk assessment. In the future they will pursue big data analytics, address issues related to computational reproducibility, to name a few areas.

Discussion Highlights

- A question was asked if they will evaluate European animal free data for regulatory applications. The Division is engaged with the Europeans, are communicating with HESI and talking about incorporating research into the Tox21 collaboration.
- A brief discussion was held on the difficulty recruiting scientist personnel especially now that FDA cannot hire someone who has not been in the US for 3 of the past 5 years. STEM activities are important, and that FDA has an activity in DC every 2 years. We need to think of the future.

There were no public comments, so the presentations continued after lunch.

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

- Dr. Heflich presented an overview of his Division and their outreach. Their strategy includes engaging other FDA product centers to set research priorities and developing better biological models for assessing human risk. Top accomplishments over the last 5 years include progress made on the *Pig-a* assay and implementation of tissue methods to test inhaled toxicants. Future directions will include the establishment or adaptation of more genetic toxicology endpoints, development of complementary rodent and human *in vitro* tissue models to improve translation and development of *in vitro* approaches for evaluation of reproductive toxicity. In the future he would like to make better use of modeling approaches.

Discussion Highlights

- A discussion ensued about the use of MPS in this division. Dr. Heflich mentioned that addition of new cells affects the stability of the system. The system they are using is stable for one year so can perform repeated treatments, etc.

Dr. Carl Cerniglia (Division of Microbiology)

- Dr. Cerniglia presented an overview of this Division and its outreach. Their strategies include 1) contribution to FDA guidelines and regulations, 2) enhancement of FDA research interactions and 3) strengthening research program management.
- The top 3 accomplishments over the last 5 years were the development of approaches to evaluate plasmid-associated antimicrobial resistance with CVM, detection of microbial contaminants in tattoo inks with CFSAN and conducting host-microbiome assessment to evaluate the effects of FDA-regulated products on the microbiome. The microbiome studies were conducted with CVM, CDER, CTP and NTP/NIEHS.
- They will build on work being done in the area of the microbiome. Collaborations with individual centers (CBER, CVM, CDER, CTP) and NTP are completed or underway.

Discussion Highlights

- The discussion centered around the identification of FDA needs and use of databases. The former is accomplished in a multi-factorial manner with discussion with PIs and the other Centers, meetings Dr. Mendrick has routinely with the heads of research at the Centers, etc. It was noted that that there is an enormous amount of sequence data and databases among centers and external groups (e.g., NARMS and CDC). This Division is working with both databases

Dr. Sherry Ferguson (Division of Neurotoxicology)

- Dr. Ferguson provided an overview of the Division and its outreach. Three top accomplishments were in the last five years were presented. 1) The receipt of US and European patents for a potential therapeutic intervention for neurological disorders using a conjugate of nicotine and nanoceria, 2) progress in pediatric anesthetic exposure assessment, and 3) recognition of the importance of microglial activation in CNS vasculature damage.
- Current projects highlighted were the assessment of the neurotoxicity of ketamine as an anti-depressant in rats (done in collaboration with CDER) and neurotoxicity of inorganic arsenic in rats (funded by NTP)
- Future projects may include assessment of the brain-microbiome connection in rats and continued examination of xenobiotic developmental neurotoxicity in zebrafish

Discussion Highlights

- A question was posed as to what is done after NCTR identifies issues such as anesthetics. How do you move it to risk assessment phase? Dr. Ferguson said this was done with CDER and they can use it for risk assessment, etc. Such studies by NCTR and others led to warnings. Clarity was given on imaging with the statement that this facility is within this division. A question was asked as to whether there are ongoing projects using MRI or PET where, for example, one can look at changes in lipid levels. Dr. Ferguson reported that imaging was done in the HESI project that was a huge dataset with multiple endpoints.
- What time frame is evaluated in developmental neurotoxicology studies? How do you consider delayed onset of effects that you may not see until later in life? The arsenic study was used as an example in which exposure begins *in utero* with further dosing upon birth until 3 weeks of age and following them until day 180. Behavioral assessment and other endpoints (e.g., brain levels of arsenic) will be studied. It is possible that long term toxicity will be missed.

Dr. William Mattes (Division of Systems Biology)

- Dr. Mattes provided an overview of his Division and its outreach. Top accomplishments in the last 5 years include a study of hepatocyte toxicity caused by small-molecule kinase inhibitors, identification of potential biomarkers of doxorubicin-induced cardiotoxicity in breast cancer patients, and examination of sex and age differences in liver mRNAs expression during the rat lifespan
- Examples of current projects include a rat model of transient and adaptive responses to hepatotoxicity (collaboration with CDER, UNC and Lilly) and evaluation of biomarkers predictive of anthracycline-induced cardiotoxicity in pediatric cancer patients (collaboration with CDER and Arkansas Children's Hospital)
- Future directions include characterization of individual iPSC-CM lines for screening and single cell RNAseq analysis to examine differences in individual cell responses to drugs

Discussion Highlights

- A question was asked if there is an enrichment step in the *E. coli* test and what type of antibodies are used. A 6-hour culture is used in some cases and the assay uses polyclonal antibodies.
- Is Maldi being used for whole body zebrafish? Yes, they do have a project studying zebrafish kidney and the whole body.
- A question as posed as to how one can handle the lack of variability in MPS given the single cell data shown. One must understand the limitations and many MPS start with primary cells. Testes system will use mouse testes and mice are individuals, so it may be necessary to develop MPS characterized from multiple individuals and cell lines.

Dr. Slikker thanked the SAB members and the representatives from other FDA Centers. He noted that NCTR described some of our projects but do not have enough time to present all our ~200 projects. These are evaluated by other FDA centers that exert effort giving us feedback. You are seeing a sampling of the projects we do.

The public meeting was adjourned at 4:06 pm

March 20, 2019. Meeting started at 8 am

RADM Denise Hinton (Chief Scientist)

- RADM Hinton congratulated Dr. Slikker for being awarded the 2019 Mildred S. Christian Career Achievement Award from the Academy of Toxicological Sciences and thanked Dr. Patri for his inter-agency efforts in nanotechnology. NCTR is the only Center at FDA that provides research to all regulatory centers in toxicology research. The OCS remains committed to support NCTR and its important work. NCTR has provided several Grand Rounds presentations including work on BPA.

- NCTR has had a leading role in, or participated in, numerous FDA working groups, including on toxicology, emerging sciences, and artificial intelligence. She recognized NCTR's role in promoting global harmonization and the standardization of regulatory science in its work with our international partners.

Dr. Carolyn Wilson (CBER)

- Dr. Wilson provided an overview of the products regulated by CBER. A regulatory challenge is that most of their products cannot be sterilized. They have an internal research group and she provided a list of their scientific expertise. She discussed collaborations with NCTR and provided examples accompanied by their potential impact on the FDA. An example is a project to detect off-target mutations of gene editing because new sensitive methods are needed. The outcome of this study will help address a significant regulatory challenge in evaluating the safety of genome editing technologies. Another example is a collaboration on MPS systems to explore spermatogenesis among multiple species.

Dr. Juan Ruiz (CDER)

- Dr. Ruiz described CDER's Research Governance Council (RGC) which oversees research functions with this Center. He described the NCTR-CDER inter-center project review process in which CDER provides NCTR feedback as to whether the project is relevant to the CDER mission. Dr. Ruiz provided some examples of collaborative projects including FDALabel, a bioinformatics tool. A graph demonstrated that NCTR is the major collaborator with CDER among the FDA Centers.

Dr. Jason Aungst (CFSAN)

- Dr. Aungst presented instead of Dr. Fitzpatrick. He introduced the MPS work being done in this Center, the FDA Roadmap (released in December 2017) and external collaborations (e.g., Tox21). Dr. Aungst discussed some research ongoing within CFSAN such as testing metals in *C. elegans*.

Dr. Selen Stromgren (ORA)

- Via telecon Dr. Stromgren introduced the mission and responsibilities of the Office of Research Coordination and Evaluation (OCDE) in ORA. She discussed their research interests (e.g., food/feed related research, medical products/tobacco related research and cross-cutting program research). Dr. Stromgren mentioned some current areas of collaboration with NCTR (e.g., nanotechnology) and future areas.

Dr. Dana van Bemmel (CTP)

- Dr. van Bemmel introduced the Tobacco Control Act, FDA's comprehensive plan for tobacco and nicotine regulation and their outreach for public comments. She provided details on their research initiatives and provided some examples of collaboration between CTP and NCTR.

Dr. Mary Allen (CVM)

- Dr. Allen introduced CVM and its Office of Research with examples of its work (e.g., NARMS, the National Antimicrobial Resistance Monitoring System). She provided examples of current collaborations with NCTR (e.g., work with gut on a chip to determine the impact of antimicrobial drug residues).
- She discussed the genetically-modified salmon. Eggs now be imported into the US. Introduced the collaborations with NCTR that include fourteen ongoing studies in areas such as the intestinal microbiome, nanotoxicology, and mechanisms of AMR.

Dr. Edward Margerrison (CDRH)

- Via telecon Dr. Margerrison presented the broad regulatory mandate of his Center and their research interests and priorities. He discussed some potential future areas of collaboration (e.g., modernize biocompatibility and biological risk evaluation of device materials).

A discussion of NCTR research was held by the SAB Members

Dr. Aschner noted that a recurring theme were alternatives and asked about FDA-wide initiatives. Dr. Mendrick described the formation of the *In Vitro* Systems Working Group under the Office of Chief Scientist which has a user group comprised by representatives from the FDA Centers that discusses such work. Dr. Wilson mentioned ICCVAM and Dr. Slikker noted the agencies involved in the National Toxicology Program: FDA, NIEHS, and NIOSH.

Dr. Stice wanted the FDA Regulatory Centers to explain their interactions between NCTR and how they define success (e.g., metrics). Dr. Wilson said that CBER looks at four areas: relevance, scientific dissemination (papers and meeting, their Science Board meetings), scientific impact (dissemination vs. uptake; use of a model by a regulated industry), and direct impact of regulatory actions (e.g., guidance documents). Dr. Ruiz noted that CDER is like CBER with outcome metrics basically weighted equally. Most important is information dissemination and guidance. They are looking at the impact that research has on speeding up the review process (e.g., providing tools to accelerate reviews). Dr. van Bemmel said CTP has an evaluation program that is similar with outcomes, but many projects do not result in papers, so their metrics includes white papers, etc. Dr. Allen said CVM has a process like Dr. Wilson discussed but their process is not as far along. They ask questions such as does it answer the question posed, what impact does it have on industry and regulation, and was there a specific impact such as guidances? Many projects are not publishable because of priority information so they consider final reports and white papers as well as peer-reviewed manuscripts. Dr. Hinton echoed this and noted that the Office of Chief Science looks at working groups to see what is happening.

Dr Slikker thanked the SAB members, the FDA representatives who attended the meeting, RADM Hinton, and Dr. Lein for chairing the SAB.

Dr. Lein thanked all for their efforts.

The public portion of the meeting concluded at 11:25 am

There was no closed session