FDA National Center for Toxicological Research

Science Advisory Board Meeting

December 3-4, 2019

These summary minutes for the December 3-4, 2019 meeting of the National Center for Toxicological Research (NCTR) Science Advisory Board were approved on December 11, 2019. I certify that I attended the December 3-4, 2019 meeting of the NCTR Science Advisory Board and that these minutes accurately reflect what transpired.

____/s/_____

Donna L. Mendrick, Ph.D.

Designated Federal Official, NCTR

____/s/_____

Gregory Lanza, M.D., Ph.D.

Acting Chair, NCTR Science Advisory Board, on December 3, 2019

____/s/_____

Michael Aschner, Ph.D.

Chair, NCTR Science Advisory Board. Chaired the meeting on December 4, 2019.

A verbatim transcript will be available and posted at the SAB meeting materials page on the FDA.gov site.

December 3, 2019. Meeting started at 8:04 am

The meeting was called to order by Acting Chair of the Science Advisory Board (SAB), **Gregory Lanza, M.D., Ph.D.,** Professor of Medicine, Cardiovascular Division, Washington University School of Medicine. (Dr. Michael Ascher, Chair of the SAB was delayed due to a snowstorm. He chaired the meeting on Dec 4, 2019)

He 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, who joined us on December 4, 2019
2. **Mary Ellen Cosenza, Ph.D., DABT,** President, MEC Regulatory & Toxicology Consulting, LLC
3. **Susan Felter, Ph.D.,** Research Fellow, Central Product Safety, Procter & Gamble
4. **Patricia E. Ganey, Ph.D.,** Professor, Department of Pharmacology and Toxicology, Michigan State University
5. **Charles Kaspar, Ph.D.,** Professor & Chair, Department of Bacteriology, University of Wisconsin
6. **Gregory M. Lanza, M.D., Ph.D.,** Professor of Medicine, Cardiovascular Division, Washington University School of Medicine

7. **Kenneth S. Ramos, M.D., Ph.D.,** Executive Director Texas A&M Institute of Biosciences and Technology, Texas A&M University
8. **John-Michael Sauer, Ph.D.**, Program Officer, Biomarker Programs and Executive Director, PSTC, Critical Path Institute
9. **Steven L. Stice, Ph.D.,** Professor, Georgia Research Alliance Eminent Scholar, Director of the Regenerative Bioscience Center, University of Georgia

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

1. **RADM Denise Hinton,** Chief Scientist, Office of the Commissioner (OC)
2. **Suzanne C. Fitzpatrick, Ph.D., DABT, ET.,** Senior Advisory for Toxicology, Center for Food Safety and Applied Nutrition (CFSAN)
3. **Madhu Lal-Nag, Ph.D.,** Program Lead, Research Governance Council, Office of Translational Sciences, 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. **Selen Stromgren, Ph.D**., Associate Director for Research Coordination and Evaluation, Office of Regulatory Affairs (ORA)
6. **Dana van Bemmel, Ph.D., MPH,** Chief, Research and Knowledge Management Branch, Office of Science, Center for Tobacco Products (CTP)
7. **Chris A. Whitehouse, Ph.D.,** Acting Deputy Director, Office of Research, Center for Veterinary Medicine (CVM)
8. **Carolyn A. Wilson, Ph.D.,** Associate Director for Research, Center for Biologics Evaluation and Research (CBER)

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, Division of Biochemical Toxicology
Carl E. Cerniglia, Ph.D., Director, Division of Microbiology
Steven L. Foley, Ph.D., Deputy Director of the Division of Microbiology
Gonçalo Gamboa da Costa, Ph.D., Division of Biochemical Toxicology
Sherry Ferguson, Ph.D., Director, Division of Neurotoxicology
Robert Heflich, Ph.D., Director, Division of Genetic and Molecular Toxicology
Manju Manjanatha, Ph.D., Deputy Director, 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
Bradley Schnackenberg, Ph.D., Associate Director, Office of Scientific Coordination
Weida Tong, Ph.D., Director, Division of Bioinformatics and Biostatistics

Dr. Lanza (Chair)

- Dr. Lanza opened the meeting by asking the SAB members, FDA representatives and the leaders of NCTR 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 2018/2019 and illustrated how the research at NCTR supports the FDA Product Centers. 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).

Discussion Highlights

- A question was raised as to how NCTR transfers knowledge outside the agency. This is accomplished through peer-reviewed publications and meetings (e.g., societies, Global Summits and the resulting report). There are additional ways to transfer information within the FDA by meetings, etc.
- One of the SAB members felt strongly that NCTR should take a more involved role in using artificial intelligence (AI) approaches on internal FDA data to predict toxicity. He noted that companies do not have the scope of data that exists within the FDA. NCTR is using aspects of artificial intelligence in tools such as FDA-Label.
- There are far fewer applications on second year for the PHCE and a SAB member asked for an explanation. There are more limited funds for starting new projects as it is necessary to continue to pay for the second-year work on the first proposals funded. A second member ask what their metrics are for success. There are yearly workshops that evaluate progress as well as regularly scheduled reports.

Subcommittee Review of the Division of Genetic and Molecular Toxicology (DGMT)

- Drs. Felter and Aschner were chair and co-chair, respectively, of the Subcommittee that met in March 2018 to review the DGMT. Dr. Felter spoke about their report. The review was conducted over two half days and posters were provided. They enjoyed the format but found it difficult to see all the posters over such a short time. Experts were assigned to each of the three focus areas. They found the research to be highly relevant, impactful and fits the FDA mission. Evident from their history of achievements is that they provide essential support to NCTR and the overall FDA. These scientists are highly collaborative and involved across FDA centers, professional societies and consensus-forming groups. Quality of their sciences is outstanding. One caution was to insure, where appropriate and feasible, the research remain hypothesis driven vs. technology driven.
- **There was unanimous approval of the report.**

Response to Subcommittee Review

- Dr. Heflich spoke to the report and thanked the subcommittee for their work. Due to the restricted time and other considerations, not all their work could be discussed and that may have led to some of their questions. He responded to comments made in the report and mentioned, for example, that they are using an *in vitro* airway model.

Discussion Highlights

- In response, several SAB members confirmed that the review was overall positive in nature.
- A discussion was held on the issue of biomarker qualification as the speed of such was questioned in the report. It was clarified that this was not meant to be specific to the CDER process but by all groups including OECD. The process for the acceptance of the *Pig-a* assay by OECD began in 2015 and is estimated to be finished in 2022.

Statement from the Chief Scientist

RADM Denise Hinton, Chief Scientist in FDA's Office of the Commissioner provided comments. She noted that NCTR's work and contributions have footprints over all of FDA and addresses top priorities. Her office has been and will continue to be fully committed to: 1. raising awareness of NCTR's scientific research and its impact on our regulatory decision-making, and 2. supporting NCTR in its work to protect public health and advance the innovative tools and approaches that are critical to FDA's predictive capability and our ability to predict risk and efficacy. She noted that NCTR personnel play leadership roles in FDA initiatives including the PHCE, Predictive Toxicology Roadmap and the Science Forum. They also are leaders and members of interagency groups looking at alternative methods such Tox21 and ICCVAM. The play leadership roles in international initiatives such as the GCRSR and internal groups (e.g., the AI Working Group and the Emerging Sciences Working Group).

FDA Center Perspectives

Dr. Carolyn Wilson, CBER, thanked Dr. Slikker and others for her invitation. She provided an overview of the products regulated by CBER and their research goals. She discussed some of the CBER-NCTR collaborations (they address CBER research goals 1 and 2) and included the names of the Principle Investigators at both centers, described the need for the research, why CBER is working with NCTR and the potential impact of the work. Examples include NCTR's expertise with lipidomics and metabolomics. She also presented some of the research being done where CBER's efforts are helping NCTR such as in the area of microfluidics. Future work may include an expanded collaboration with the use of NCTR's air-liquid-interface (ALI) human *in vitro* airway tissue model to study a variety of issues, such as allergen interactions, mucosal vaccine/adjuvants, and respiratory viral pathogenesis

Discussion Highlights

- There was no discussion

Dr. Madhu Lal-Nag, CDER, thanked Drs. Slikker and Mendrick for the opportunity to present their work. She described their Regulatory Governance Council (RGC), its strategic plan, the process for reviewing NCTR proposals, and provided several examples of the impact of CDER-NCTR collaborations. The mission of RGC is to enhance CDER's research capabilities and impact awareness. There are 31 active projects with NCTR, and she provided one example; the effect of opioid exposure on developing brains which may contribute to more precise recommendations regarding the safety of opioid use in pregnancy. She said it would help to have NCTR more involved in the SPaRC (Science Prioritization and Review Activities) initiative.

Discussion Highlights

- Questions focused on the recent CDER reorganization and its potential impact on the RGC and what hindrances there may be in incorporating NCTR more into their efforts. Dr. Lal-Nag

responded that both aspects were not hindrances. RADM Hinton noted that such engagement is welcome.

Dr. Ed Margerrison, CDRH, presented the regulatory mandate of his center noting they are responsible for 190,000 types of products. Usually they do not oversee products that have a chemical or biological reaction. They often are the recipient of technology coming from other areas that are now being used in medicine. An example is AR/VR (augmented and virtual reality) which came from the gaming industry but now is in medical devices that today aids a physician but, in the future, will be making diagnoses. He provided a list of broad research interests. He noted that FDA has an excellent internal group on computational modeling comprised of representatives from all FDA Centers. Potential areas of future collaboration with NCTR include materials performance. Two of CDRH's major interests are to find ways to stimulate innovation and identify what happens to materials in the body.

Discussion Highlights

- Questions from the SAB focused on the electronic transfer of multiple types of patient data from institute to institute and cybersecurity concerns. CDRH is involved multiple aspects including in interoperability (that is, between machines), data integrity, etc. CDRH is enormously involved in cybersecurity given the potential of hacking into devices such as a recent public example of hacking into a pacemaker. Manufacturers seem happy to work with CDRH and CDRH has a division focused on cybersecurity.

There were no comments in the public session, so the meeting continued.

Dr. Suzanne Fitzpatrick, CFSAN, discussed their reassessment of the use of dogs for food and color additive safety assessments. They concluded that "rodent studies combined with ADME data could be sufficient to evaluate the safe use of food and color additives." She described their work on Read-Across, their expanded decision tree, assessment of mixtures of metals, and some work being done by FDA with alternative models such as organs on a chip.

Discussion Highlights

- There was a brief discussion about the PFO compounds under investigation

Dr. Dana van Bemmel, CTP, provided an overview of tobacco regulation and how some of their research interests align with NCTR. These include in vivo, in vitro, and alternative toxicity assessments and biomarkers discovery. She provided a few examples of completed collaborations and how they benefited CTP's mission, ongoing projects and future endeavors. Data drives decisions that help CTP achieve its mission. One past collaboration studied harmful and potential harmful constituents in tobacco smoke using a bioinformatics approach. It was found that 47% of tobacco smoke constituents had limited scientific data demonstrating that there are data gaps even in smoke. Potential areas of further collaboration include studying toxicity of flavors in tobacco products.

Discussion Highlights

- There was no discussion

Dr. Chris Whitehouse, CVM, described their regulatory mandate and collaborations with NCTR in areas as broad as nanotoxicology and antimicrobial resistance. He also provided the impact of these collaborations.

Discussion Highlights

- There was a question about their NARMS database and whether they also used the CDC database for gene makers for antimicrobial resistance and whether the latter was available to the public. Yes, it is.

Dr. Selen Stromgren, ORA, provided the regulatory mandate of ORA, their research landscape and outcomes. They have >5000 employees; only CDER is larger. Twenty-five percent of their personnel is a laboratory workforce; the rest are inspectional. Since their research is very applied and comprised of method development and validation to support regulatory testing, their research portfolio does not get high visibility, so they are working to better showcase their impact at the agency level. She provided some examples of current collaborations between ORA and NCTR and potential future work. One example is developing a machine learning approach to identify some common filth elements (insect fragments, hair, etc.) in food products. There is a nanotechnology core facility shared by NCTR and ORA on the NCTR/Arkansas Regional Laboratory campus.

Discussion Highlights

- A brief discussion was held as to different approval standards employed by other countries' regulatory bodies. This is why a drug approved in EU for instance is not automatically considered approved in the US as well. There are global conferences for different regulatory bodies to get together and discuss their priorities to try to move towards harmonized standards.

Presentations from NCTR Research Divisions

Dr. Gonçalo Gamboa da Costa, Division of Biochemical Toxicology, described their staff, outreach and mission. The top three accomplishments during 2019 included the publication of a manuscript describing the findings of the core study of the CLARITY-BPA consortium, in-depth studies of the pharmacokinetics of arsenic, and epigenetic mechanisms that may underly the organ-specific carcinogenesis of acrylamide. He provided some details on current projects including tattoo pigments (in collaboration with CFSAN) and Pegylated biopharmaceuticals (collaboration with CDER and CBER). Some future projects under consideration include 1) an arsenic bioassay in collaboration with CFSAN and 2) research to help determine the genomic and genetic determinants of susceptibility to non-alcoholic fatty liver disease and identify novel biomarkers for diagnosis and monitoring.

Discussion Highlights

- There was a discussion of NAFLD (non-alcoholic fatty liver disease) related to its fit within the division and the use of the resulting data. It was noted that NCTR division perform research broader than answering immediate needs of Centers. There is no therapy for NAFLD, and diagnosis is difficult. One objective is to identify possible screening mechanisms (any changes in blood chemistry, for example) to enable earlier diagnoses.
- A question was asked as to how the pigments were selected for the tattoo study. The specific azo pigments were selected because they are commonly used because of their bright colors. In response to a question it was confirmed that a toxicology study will be performed if the earlier studies show distribution to the fetus.
- There were questions on the pegylated study such as to why PEG is used alone while the protein it is coupled to might drive the *in vivo* localization. The use of PEG alone was determined to be the best approach for these initial studies, in order to avoid potentially confounding immunogenic effects of a specific pegylated protein. Follow up studies may use protein-conjugated forms. Follow up studies will use protein-conjugated forms. Other concerns expressed included the use naïve rats, yet women are exposed to PEG in cosmetics and its

possible potential to form micelles. It was suggested that the nanotoxicology core facility be asked to evaluate this.

Dr. Weida Tong, Division of Bioinformatics and Biostatistics, provided some details on the division staff, a division overview and mission. The division does not perform wet lab work. They have 4 branches: bioinformatics, biostatistics, R2R and scientific computing. Of their personnel, 40% is focused on research and 60% on support/service. Research is focused on conducting integrative bioinformatics and biostatistics research to support FDA's mission of improving safety and efficacy of FDA-regulated products. (Their service/support function includes center-wide infrastructure and bioinformatics-specific support.) A support example is the development of FDALabel to manage FDA drug labeling data to support drug review and regulatory applications. This work was done in partnership with CDER.

Their top three research accomplishments were in the areas of genomics, research into drug-induced liver injury using several AI analytical approaches, and a drug safety challenge. The former is related to a long-standing consortia activity. They now are on the 4th project (cancer genomics, reproducibility and epigenomics). Future work will include a collaboration with PrecisionFDA in the Office of the Chief Scientist, continued work with big data analytics to help reviewers, investigation of real world data, etc.

Discussion Highlights

- There was appreciation by some SAB members as to the how this program has evolved over time. It was suggested that Dr. Tong clearly define AI, machine learning and other terms as audiences may be lost.
- A question was raised as to the clarity of DILI. There are many sources of information that leads to a lot of disagreement. Researchers from this Division used labeling document to determine if a drug caused DILI or not and his work was published in 2011. Five years later they performed a causality assessment and published that work. DIList is also based on drug labels but now includes drugs marketed in Japan and other countries, for example.

Dr. Manju Manjanatha, Deputy Director, Division of Genetic and Molecular Toxicology, provided an overview of their staff, outreach, mission and vision. Their research strategies include the engagement of FDA product centers, and other government entities to set research priorities in the area of genetic and molecular toxicology. Their top three accomplishments were progress on the *Pig-a* assay, identification of mutations with the greatest carcinogenic impact in specific human tissues, and a screen of genetic toxicity using metabolically competent human cells and a high throughput/high content method. Ongoing projects include developing a panel of disease-relevant molecular and physiological endpoints to evaluate toxicity in organotypic models, creating a panel of *in vitro* approaches for evaluating reproductive toxicity, and collaborative work using the *Pig-a* assay in patients receiving chemotherapy. He also listed some future projects such as developing *in vitro* approaches for evaluating reproductive toxicity including germ cell mutation.

Discussion Highlights

- The discussion focused on where NCTR is with *in vitro* to *in vivo* extrapolation and how that might inform doses chosen for in vitro or organoid testing. Several NCTR principle investigators are working on this alone and in collaboration with Regulatory Centers.
- A question was posed on the zika virus project. It was explained that FDA's Medical Counter Measures group within OCS has been speaking with a member of this division to use their TissUse system as there is a general interest in *in vitro* approaches to study viruses that hide out in the reproductive system. Zika and Ebola viruses are two examples.

The public meeting was adjourned at 4:55 pm

December 4, 2019. Meeting started at 7:59 am

Dr Steven Foley, Deputy Director, Division of Microbiology, described the division staff, outreach, mission, vision and strategies to meet this mission. The focus areas of accomplishment 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 virulence mechanisms. Details of all three accomplishments were provided. Future research strategies were discussed.

Discussion Highlights

- A discussion focused on the study of tetracycline, after acute or chronic exposures, on the permeability of human colonic epithelial cells. A discussion focused on a potential mechanism of action. There are several theories and the Division is working on RNA sequencing efforts to look at gene expression. They see the same effect with some other antibiotics that target bacterial ribosomes.
- A question was posed as to the study of fecal transplants. In the clinic today they are using donor material but there may be a move to isolated bacteria in the future. It was suggested that NCTR has the expertise to look at the use of isolated bacteria
- Many of the Regulatory Centers has efforts in the area of microbiology. Good communication results in NCTR addressing their data gaps and not duplicating their work.
- Studies are underway to look at microbial contamination of tattoo inks. This led to a question as to the incidence of acute and chronic infections. When one gets a tattoo, they are warned about acute infections and it is a problem. Too little work has been done to look at chronic effects.

Dr. Sherry Ferguson, Division of Neurotoxicology, described the division staff, outreach, mission and vision. The top three accomplishments in 2019 were the MRI of nonhuman primates previously exposed to methylphenidate, expansion of *in vitro* work (e.g., using microphysiological systems), and increased responsiveness to agency-specific needs. She provided examples of future collaborative work, and directions.

Discussion Highlights

- The capability of our imaging suite was a brief subject of discussion. It was suggested that we purchase a clinical scanner that offers some additional imaging options.
- There have been studies with cell stretching models to simulate traumatic brain injury. Does the amount of stretch replicate the experience in humans? It is very difficult to measure it in human brain although up to 60% stretch has been shown in humans.
- Studies are being done to look at fluid biomarkers within the division and with, for example, the Health and Environmental Sciences Institute (HESI).
- There was a question regarding the relevance of an *in vivo* traumatic brain injury model to the FDA. Such models will enable the detection of vulnerable populations that will help reviewers when drugs are submitted for approval.

Dr. William Mattes, Division of Systems Biology, described the division staff, outreach, mission and vision. He listed collaborations of note both with FDA Centers and the USDA. He provided details on the goals, strategies, and themes of this division. He provided selected accomplishments in 2019 including the development of an *in vitro* testis model, lipidomic tissue analysis and identification of plasma protein biomarkers in a mouse model of doxorubicin cardiotoxicity. Examples of current projects the prediction of tyrosine kinase inhibitor induced cardiotoxicity using patient-specific induced pluripotent stem cell derived cardiomyocytes, a technology that can rapidly identify adulterated drugs, and molecular modeling of opioids.

Discussion Highlights

- If you know the mechanism in humans, can one translate to animal and then to a cell-based system? This will have the most benefit and impact. A challenge is how one can take one model and connect to another.
- Related to the patient-specific induced pluripotent stem cell derived cardiomyocytes study, could differences be due to cell line derivation or actual individual-based differences? Both are possible although some drugs show no individual variability.
- A question was asked as to whether *in vivo* studies are being done to look at earlier biomarkers of cardiac injury caused by doxorubicin. The table shown illustrates biomarkers seen before dosing suggesting these might identify susceptible individuals. There is a published paper on cytokine levels before drug administration suggesting pre-existing inflammatory differences may help drive the toxicity. There was enthusiasm expressed to continue in this direction as therapies are getting better so now there is more concern about long term adverse events.
- A discussion was held as to how one can translate this great science into regulatory tools for decision making. NCTR does not always develop a specific tool. For example, many Centers are becoming familiar with tools such as microphysiological systems, so we understand the technology when data comes in for a review. There was a brief discussion as to how one could qualify assays.

A discussion of NCTR research was held by the SAB Members

Comments from the SAB and FDA Center representatives included the following:

- NCTR continues to demonstrate more collaborations within FDA and NCTR every year. The scope, expertise and collaborations are outstanding. AI is important for the early prediction of adverse events and it was encouraged that such work be continued.
- The microbiology work is focused on key areas for the near and long term.
- NCTR has led the way showing non-linearity in animals, etc. There is a need for such studies to be done with *in vitro* systems.
- A way to present metrics on work done at NCTR beyond papers and presentations should be considered
- Although the link of our research to toxicology and regulatory needs are clear in most cases, it should be clearly expressed in all science presented. NCTR should differentiate itself from other groups.
- There are always communication challenges.
- It would be better to have more clarity on how NCTR selects studies and the questions you want to ask vs. a focus on methods. Methods should support the question instead of driving the science.

- Important to build on *in vitro* work to extrapolate to *in vivo* using MPS, for example.
- FDA Centers have benefited from work done at NCTR but not all at FDA headquarters know of NCTR's capabilities.

Dr. Slikker thanked the SAB members and the representative from the other FDA Centers for their participation. He also thanked the support from our Chief Scientist. NCTR is making good progress but still has some areas in need of improvement.

Dr. Aschner also thanked the SAB and the FDA Center representations.

The public portion of the meeting concluded at 11:14 am