FDA National Center for Toxicological Research

Science Advisory Board Meeting

November 6-7, 2017

These summary minutes for the November 6-7, 2017 meeting of the National Center for Toxicological Research (NCTR) Science Advisory Board were approved on November 18, 2017. I certify that I attended the November 6-7, 2017 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/ucm578551.htm

November 6, 2017. Meeting started at 8:05 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. **Elena Fuentes-Afflick, MD, MPH,** Professor and Vice Chair of Pediatrics/Vice Dean for Academic Affairs, University of California, San Francisco. (She attended part of Day 1 via phone)
4. **Diwakar Jain, M.D., FACC, DRCP, FASNC,** Professor of Medicine (Cardiology), Director of Nuclear Cardiology, Westchester Medical Center
5. **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 in Saint Louis
6. **Pamela J. Lein, Ph.D.,** Vice Chair, Department of Molecular Biosciences, Professor of Neurotoxicology, UC Davis School of Veterinary Medicine
7. **Suresh Pillai, Ph.D.**, Professor of Microbiology, Texas A&M University
8. **John-Michael Sauer, Ph.D.,** Biomarker Programs and Executive Director, Predictive Safety Testing Consortium (PSTC), Critical Path Institute, Research Professor, Department of Pharmacology, University of Arizona College of Medicine (Consumer representative)
9. **Steven L. Stice, Ph.D.,** Professor, University of Georgia; Georgia Research Alliance Eminent Scholar, Director of the Regenerative Bioscience Center

FDA Representatives:

1. **Cathy Backinger, Ph.D., MPH,** Deputy Director for Research Office of Science, Center for Tobacco Products (CTP)
2. **Robert Dorsam, Ph.D.**, Supervisory Pharmacologist, Division of Clinical Review, Office of Generic Drugs, Center for Drug Evaluation and Research (CDER)
3. **John S. Graham, Ph.D., MBS, DABT,** Director of Research, Center for Veterinary Medicine (CVM)
4. **Karen Hatwell, Ph.D.,** Science Advisor for Chemistry, Office of the Center Director, Center for Food and Applied Nutrition (CFSAN)
5. **Adebayo Laniyonu, Ph.D.**, Supervisory Pharmacologist, Division of Medical Imaging Products, Office of New Drugs, Center for Drug Evaluation and Research
6. **Sean Linder, Ph.D**., Senior Science Advisor, Office of Regulatory Affairs/Office of Regulatory Science (ORA)
7. **Ed Margerrison, Ph.D.,** Director, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health (CDRH)
8. **Carolyn A. Wilson, Ph.D.,** Associate Director for Research, Center for Biologics Evaluation and Research (CBER)

Other Government Officials:

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

National Center for Toxicological Research (NCTR) Scientific Leaders and Speakers:

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
Carl Cerniglia, Ph.D., Director, Division of Microbiology
Robert Heflich, Ph.D., Director of the Division of Genetic and Molecular Toxicology
Merle Paule, Ph.D., Director, Division of Neurotoxicology
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 (alignment with FDA's Advancing Regulatory Science Plan, enhance intra-FDA collaborations and promote global interactions in regulatory science). He provided three top accomplishments in 2016/2017 and illustrated how the research at NCTR supports the FDA Product Centers and ORA. He touched on succession planning needs and provided details of a nascent FDA Virtual Center on Maternal and Perinatal Medicine, Developmental Toxicology and Modeling.

Discussion Highlights

- Dr. Pillai asked about the work with opioids and Dr. Slikker explained that they are using an *in vitro* neural stem cell approach. Dr. Lanza discussed the challenges of translating *in vitro* and animal models to human. Dr. Slikker noted that one can evaluate several different animal models and a limited number of human samples to confirm the data as was done with bisphenol A. Modeling can provide data in areas where you cannot get human samples and *in vitro* human-derived stem cells can enable the use of human material but, of course, they have disadvantages. Dr. Stice asked how projects are initiated and Dr. Slikker explained that they might come from a regulatory center request, a NCTR principle investigator (PI), etc. There are points of contact within each Center that Dr. Acosta works with to determine if a project should move forward. In response to a question of how projects are prioritized by Dr. Lein, Dr. Slikker said that the protocols that are approved are prioritized by the Division Directors based on FDA impact.

Subcommittee Review of the Division of Systems Biology

- Drs. Pillai and Jain were chair and co-chair, respectively, of the Subcommittee. Dr. Pillai explained that there were a few thematic areas within the Division. They have focused on developing and evaluating biomarkers and the Subcommittee felt that the organization structure was not adequately addressing the scientific potential. There is a need to integrate many of these areas within the division. The speakers had posed research questions the Subcommittee did their best to answer them. They suggested that the Division spend more time validating the biomarkers they have discovered rather than pursuing new ones. Dr. Jain discussed the doxorubicin study and felt it was good to start with animal studies but one needs to examine the genetic susceptibility as they see variability in patients. Thus, they need to follow up with clinical studies (as is the case with the proposed work on tyrosine kinase inhibitors). He felt it otherwise was a very well-conceived program and will provide a large amount of information. Dr. Pillai noted that Dr. Varma's work on the obesity model generated a large amount of enthusiasm. Overall, they felt the Division has deep expertise in many areas and needs some integration and to work with NCTR's Microbiology Division on their bacterial projects.
- There was approval of a modified report that will include a summary paragraph. The approval was unanimous.

Response to Subcommittee Review

- Dr. Mattes could not attend the meeting as he was at the American College of Toxicology meeting in part to recruit new members to the Division to improve integration as requested by the Subcommittee. In his place, Dr. Schnackenberg responded and some of the highlights are detailed here. They are reviewing the divisional structure based on the Subcommittee's feedback. There will be more focus on validation of candidate biomarkers and discussions have begun with CDER's Drug Development Tool Qualification team and the Predictive Safety Testing Consortium of the Critical Path Institute. To this end, context of use statements have begun to be written as they will guide biomarker qualification. The Subcommittee suggested an increased focus on clinical studies and context and the Division has begun to examine proteomics results from a clinical study of doxorubicin-treated breast cancer patients and established a collaboration with the pediatric oncology group at Arkansas Children's Hospital. The Subcommittee was very excited about the obesity model and asked that the Division consider studying drug efficacy as well as safety. A collaboration with CDER has been established to address a variety of obesity-dependent endpoints.

Discussion Highlights

- Dr. Jain (Subcommittee Co-Chair) noted that he was happy with the response to their review. Dr. Pillai was happy to learn that NCTR was sharing a Fellow with the Center for Food Safety and Applied Nutrition to move RAPID-B forward. There was discussion about modeling and biomarker qualification. Dr. Sauer asked about a clinical strategy for biomarkers and Dr. Schnackenberg reported that animal studies are used for discovery and then selected biomarkers explored in clinical samples with local collaborators. Such was done for acylcarnitines discovered originally in rats and then assessed in human samples.

Dr. Frederick Beland (Division of Biochemical Toxicology)

- Dr. Beland presented an overview of his division and their collaborations within and outside the FDA and global leadership. Their focus is to characterize toxicity and carcinogenic nature of compounds of interest to the FDA. To this end they perform bioassays, mechanistic studies, and computational modeling.
- He discussed multiple projects including 1) an ongoing arsenic study to address the concern of exposure during perinatal life stages, 2) a project that will look at mutational signatures of tumors induced in rodents by acrylamide and glycidamide and compare these signatures with those of human tumors in published databases and 3) the use of physiologically based pharmacokinetic modeling to examine the risk of exposure to thyroid active-chemicals during pregnancy.
- In collaboration with scientists from CDER and CBER, his division will examine the long-term effects of exposure of Pegylated (PEG) polymer. Some drugs and biologics are non-covalently bound to PEG. The issue is whether the accumulation of PEG and the formation of cellular vacuoles pose an adverse effect when such compounds are used chronically or in pediatric patients. The protocol outlined in these slides has been modified recently following a discussion of the committee.
- A new collaboration with CFSAN is looking at two dietary supplements (nattokinase and lumbrokinase) ingested for claimed benefits for the circulation. The concern is that they will increase the risk of bleeding. In another collaboration with CFSAN, they will develop a new mouse model to study the effect of exposure to ultraviolet radiation in the presence of a photo-

co-carcinogen. Such a model would reduce the use of animals to examine novel agents for such an adverse effect.

Discussion Highlights

- There were many questions about the PEG study and Dr. Beland noted that it is being done to answer the needs to CDER and CBER. Some of the questions centered around potential immune activation and it was noted that the production of antibodies to PEG will be assessed. There was a question raised as to the output of the study. Dr. Beland noted that this project is focused on addressing a regulatory need of CDER and CBER. They hope to publish the results as well so that the results can be disseminated.
- Another area under discussion was the aforementioned acrylamide study. For example, Dr. Felter noted that acrylamide is associated with multiple tumor types and asked if the expression will be examined in multiple tumor types and non-tumor tissues from the same animal. Dr. Beland noted that these are expensive studies and assessment will be performed as budget enables.

<u>Dr. Robert Heflich (Division of Genetic and Molecular Toxicology)</u>

- Dr. Heflich discussed collaborations and global leadership outreach for his division. The Division's mission is to improve public health by providing the agency expertise and tools to assess genetic risk and strengthening knowledge integration into regulatory decision making. His goals are to respond to agency needs with research, assay development and the establishment of new paradigms that integrate measures of genetic risk with biomarkers of toxicity. He discussed ongoing work to develop better biological models using *in vitro* organotypic models, primary cells, *C. elegans*, etc. Detail on their human airway *in vitro* model was provided. Ongoing and proposed projects were described in assessing inhalation toxicity using *in vitro* approaches and transgenic rats.
- To provide more comprehensive approaches for monitoring genetic variation, Dr. Heflich described ongoing and proposed projects. An example of the latter is a high fidelity next generation sequencing and whole genome clone analysis.

Discussion Highlights

- There were many questions regarding his work on germ cell mutations. For example, Dr. Felter asked if he wanted to focus on germ cells instead of somatic cells as he feels that the former are more susceptible. Dr. Heflich said yes and noted that he considers germ cell mutagenesis an endpoint. Mutation in somatic cells can lead to a phenotype in adults. However, if there is a germ cell mutation, there could be hundreds of diseases associated with them.

There was a break for lunch and then a public comment period. There were no public comments so the presentations continued.

Dr. Carl Cerniglia (Division of Microbiology)

- Dr. Cerniglia presented the mission of his Division. It is to serve a multipurpose function with specialized expertise to perform fundamental and applied research in microbiology in areas of FDA's responsibility in toxicology and regulatory science. His vision is to be a valued resource in advancing regulatory science research for the FDA. He presented collaborations and global outreach of his Division. His Division has a broad portfolio on research such as examining the impact of antimicrobial agents, etc. on the microbiome, the development of methods to detect microbial contamination, and the determination of antimicrobial resistance and virulence mechanisms of foodborne and other pathogens.
- He described three top accomplishments. These include work on tattoo inks, assessment of the impact of xenobiotic compounds on the gastrointestinal microbiome and immune response, and the evaluation of antimicrobial veterinary drug residues in foods on the human intestinal microbiota and intestinal epithelium.
- Future strategy for this division includes continued emphasis to understand the impact of FDA-regulated products on the microbiome, advancement of new scientific approaches to determine the impact of microbial contaminants in FDA-regulated products and to continue to conduct research for safety assessment through the integration of systems biology approaches.

Discussion Highlights

- Dr. Pillai asked if the approach was a focus on individual organisms or in context of the whole microbiome. Dr. Cerniglia responded that they think of the microbiome as a community but with next generation sequencing, one can get to strain level. Dr. Pillai asked why a study of antibiotic effects was done with tetracycline instead of the newer, synthetic antimicrobials. Dr. Graham, CVM, noted that this project was of interest because tetracycline is used in food animals.
- A discussion was held on microbial fecal transplants. The Division is working with CBER in this area and trying to understand the mechanisms. Dr. Cerniglia noted that the microbiome can persist for life while a drug has a unique clearance characteristic.

Dr. Merle Paule (Division of Neurotoxicology)

- Dr. Paule provided the mission and research themes of his division. They are "… to develop and validate quantitative biomarkers and identify biological pathways associated with the expression of neurotoxicity…….employing fundamental research efforts in several focal areas." They use approaches ranging from *in vitro* methods, to zebrafish to behavioral testing in humans. He profiled their outreach ranging from NCTR and FDA to other government agencies and academia. He also provided examples of global leadership and outreach.
- He delineated three recent accomplishments (expansion of their blood-brain-barrier on a chip, progress on biomarkers of neurotoxicity using MRI T2 images and studying sevoflurane-induced cognitive deficits in laboratory animals).
- He provided examples of further directions in bioimaging and using *in vitro* human neurons to study Parkinson's type damage.

Discussion Highlights

- There were some questions from Dr. Aschner regarding the potential of iron to create background issues in T2. Dr. Serguei Liachenko in this division explained that iron contributes to the signal. Dr. Lein commented on the usefulness of CLARITY and Dr. Stice concurred.

Dr. Weida Tong (Division of Bioinformatics and Biostatistics)

- Dr. Tong described the three functions of his Division (service, support and research) and provided some examples of support such as supporting Data Analysis Search Host Tool and FDALabel for CDER. The Mission of this Division is to provide research and support to NCTR and FDA scientists and to ensure their activities are related to FDA's review process. Their research using bioinformatics and biostatistics is to support FDA's mission of improving the safety and efficacy of FDA-regulated products. He provided examples of global leadership and outreach
- Dr. Tong presented details on three selected research accomplishments (MAQC, LTKB and their work on rare diseases). He then went on to describe some current projects including SEQC2 which is comprised of representatives of each FDA Center and ORA, companies, academia, etc.
- Future directions include integrating LTKB models into the review process, continually develop big data analytics, and conduct crowdsourcing and community-wide projects to assess emerging methodologies.

Discussion Highlights

- Dr. Suresh commented on the nice overview and asked if they have reached out to Google and Facebook about machine learning. Dr. Tong answered that they have not. Dr. Laniyonu, CDER, thanked them for their service work in support of CDER reviewers. Dr. Lein asked about career advancement paths. In response, Dr. Slikker described the peer review process and asked for comments in regards to those projects that require many investigators, etc. Dr. Lein noted that it is getting difficult in academia as well and that they are coming up with creative solutions. She suggested Dr. Slikker work with academia on this and to look at individuals' contribution and their impact on the FDA.

The public meeting was adjourned at approximately 4:30 pm

November 7, 2017. Meeting started at approximately 8 am

Dr. Carolyn Wilson (CBER)

- Dr. Wilson described the complex products regulated by CBER and presented some detail on vaccines and the blood supply. She mentioned CAR T-cell therapy as an example of advanced therapies at the leading edge. Challenges for CBER include preparing for new and evolving technologies, continuous manufacturing, stem cell derived products and cell-device combinations. She also presented CBER's Research Goals.
- Dr. Wilson described some of the ongoing collaborations with NCTR (e.g., bioreactor model to simulate *C. difficile*-host interactions, ribosome profiling). She also noted several collaborations in which CBER is assisting NCTR (e.g., functional screening of candidate molecules identified by NCTR SDAR for anti-trypanosomal activity)

- Other CBER-NCTR collaborations include studies of pathogen detection in fecal microbiome transplants and she explained the value of working with NCTR. Existing methods tend to detect high level bacterial infections while this assessment needs to be more sensitive in assessing fecal microbiome transplants.

Discussion Highlights

- Dr. Lanza asked about the ribosome profiling and whether it has been looked at in insulin. CBER regulates recombinant proteins that are blood derivatives so are looking at it in these products. They have not looked at smaller molecules. Dr. Pillai asked about their work on a Norovirus vaccine and Dr. Wilson noted that a new hire will be looking at this.

Dr. Robert Dorsam (CDER)

- Dr. Dorsam showed similarities and differences in the risk benefit calculations between the Office of New Drugs and Generics. 90% of prescriptions are for generics and thus are important for public health. They do not study the safety of the active ingredient as that was assessed in the original approval; instead they focus on formulation components. There must be therapeutic equivalence with the brand name drug and sometimes just looking at blood levels is insufficient.
- GDUFA supports research to develop new approaches to resolve complex generic drug development or review issues. Over 100 external projects have been supported and each year the Office of Generic Drugs hosts a public meeting to identify research priorities. Examples include looking at complex active ingredients, routes of delivery and tools and methodologies for bioequivalence.
- There is a public access excipients browser that provides access to chemical structures of FDA approved excipients (http://excipients.ucsf.bkslab.org/). One can computationally screen excipients against known pharmacological targets and test these predictions against assay results.

Discussion Highlights

- Questions were delayed until after the Center presentations were completed

Dr. Ed Margerrison (CDRH)

- Dr. Margerrison put CDRH in perspective in terms of their regulatory purview and mission. He stressed that CDRH facilitates medical device innovation. The Office of Science and Engineering Labs at CDRH works to ensure readiness for emerging and innovative medical technologies, develops appropriate evaluation strategies, creates accessible and understandable public health information and delivers timely and accurate decisions for products across their life cycle
- Areas of potential interest include computer modeling and simulation and the safety of nickel and other metal ions. There is ongoing research in modeling depolarization of the heart and looking at potential safety issues of nickel ions released from devices.
- CDRH can facilitate innovation as they have a vast store of prior data. They have made the first data set publicly available to be used by FDA and industry
- More than 80% of device companies have less than 50 staff and he wants to build a scientific bridge with the small, innovative companies where so many new products will be designed.

Discussion Highlights

- Questions were delayed until after the Center presentations were completed

RADM Denise Hinton (Acting Chief Scientist)

- She called into the meeting to provide an overview of NCTR. She noted that FDA is a science based agency and NCTR collaborates across the agency and the globe. NCTR partners with regulatory centers to provide research data to address their data gaps. Examples include the ongoing gadolinium study, arsenic, etc. NCTR scientists are evaluating new technologies to enable faster and better evaluation of regulated products. She noted that the Commissioner and herself are both pleased to see the development and growth of the FDA Virtual Center on Maternal and Perinatal Health, Developmental Toxicology and Modeling.

Discussion Highlights

- Dr. Lein asked for RADM Hinton's perspective on what she sees as emerging needs for which NCTR might be uniquely positioned. RADM Hinton mentioned areas such as the virtual center, exploring predictive models and looking beyond solely using animal models.

Dr. Karen Hatwell (CFSAN)

- Dr. Hatwell provided CFSAN's mission. CFSAN, in conjunction with the Agency's field staff, is responsible for promoting and protecting the public's health by ensuring that the nation's food supply and cosmetic products are safe and properly labeled. She provided an overview of CFSAN-regulated products which are wide-ranging.
- She noted that they are working on a new five-year strategic plan. At next year's meeting, she hopes to discuss this plan and how they are working with NCTR. Their research supports its science-based regulatory mission and focuses on microbiology, chemistry and toxicology. Part of this is knowing what hazards are in our food. A lot of issues with food borne pathogens. They have spent a lot of time on whole-genome sequencing. Their toxicology group has started to explore organs on a chip.
- She provided an overview of some collaborative research with NCTR.

Discussion Highlights

- Dr. Lanza asked about nutraceuticals particularly beet supplements taken by runners, etc. especially if the runners are already on nitrates. Dr. Hatwell noted that dietary supplements are a difficult area. Dr. Lanza is very worried about batch to batch variations.
- Dr. Pillai asked about the Centers of Excellence mentioned by Dr. Hatwell.

Dr. Cathy Backinger (CTP)

- Dr. Backinger provide a brief history of the newest FDA Center and a list of the diverse tobacco products regulated by her center
- Tobacco cannot be regulated using FDA's traditional safe and effective standard. They must take into account the benefits and risks to both users and non-users of tobacco products and assess the net population-level health impacts of such products

- FDA envisions a world where cigarettes would no longer create or sustain addiction. Nicotine is at the center of their regulatory effects. FDA is seeking comments on issues in the evolving tobacco marketplace such as the roles flavors may play in attracting youth
- CTP funds research through collaborations with federal agencies and contracts with non-HHS organizations that have needed expertise. She provided an overview of some NCTR projects that are informing CTP

Discussion Highlights

- Dr. Pillai asked if CTP is regulating THC as it is being used in electronic devices. Dr. Backinger clarified that the tobacco funds can be used only for tobacco research.

<u>Dr. John Graham (CVM)</u>

- Dr. Graham described the mission of the Office of Food and Veterinary Medicine to promote public health by preventing foodborne illness, fostering good nutrition and improving the safety and efficacy of animal health products. The CVM mission is to protect human and animal health. He heads CVM's Office of Research and their mission is to support the mission by providing meaningful research to support regulatory decisions
- He provided six FY17-18 key initiatives and an overview of CVM's staff and research focus
- Dr. Graham discussed Vet-LIRN which promotes animal and human health by collaborating with veterinary diagnostic laboratories to investigate CVM regulated products. He also described the National Antimicrobial Resistance Monitoring System which provides data on the extent and temporal trends of antibiotic resistance in enteric bacteria. This collaboration involves FDA/CVM, CDC and the USDA
- He provided an overview of the Division of Animal and Food Microbiology, Division of Residue Chemistry and the Division of Applied Veterinary Research
- Dr. Graham provided examples of ongoing collaborations with NCTR and a potential area of future collaborations (ADME of compounded or unapproved drugs).

Discussion Highlights

- Questions were delayed until after the Center presentations were completed

<u>Dr. Sean Linder (ORA)</u>

- Dr. Linden provided an overview of ORA's research. ORA's Office of Regulatory Science has laboratory facilities across the US and has recently created a new Office to coordinate all research activities. The Office of Research Coordination and Evaluation was a result of the Agency's program alignment efforts will allow ORA to directly and efficiently engage the Centers to identify and execute applied research to meet the Agency's regulatory mission.

Discussion Highlights

- Questions were delayed until after the Center presentations were completed

Discussion

Dr. Lein opened the discussion by the SAB members with input by the FDA representatives. Dr. Pillai asked about publications generated by NCTR studies and Dr. Graham responded that both Centers with interest review them even if the affected Regulatory Center did not actively participate in the research. Dr. Lanza asked Dr. Dorsam about the tolerance of generics and he responded that it might be dependent on the endpoint and sensitivity but typically between 85-115% is an acceptable range for the main endpoints for bioequivalence. Dr. Lanza ask Dr. Linder about unmet needs for public safety that they are pursuing. Dr. Linder noted that they are taking an active role in the opioid issue and misbranded drugs as two examples.

Dr. Stice asked about commonality between the human and animals in their interest in cell therapies. Where is NCTR in this field? Dr. Wilson (CBER) responded that there is an active collaboration between CBER and CVM to learn methods to evaluate stem cells. They are focused on using stems cells as medical products and are focused on methods to evaluate them as products versus the use of stem cells as toxicity test systems which was Dr. Stice's question. Dr. Stice asked how they use bio-imaging and Dr. Wilson responded that they have relied heavily on NCTR's bio-imaging lead, Dr. Liachenko's expertise in MRIs. They are trying to use MRI to track stem cells *in vivo*. Dr. Graham noted that their research in stem cells also is focused on their use as a treatment. We are focused more on the manufacturing of these products as they start out as very heterogeneous. There is a need to define requirements.

Dr. Pillai notes that next generation sequencing technology is changing rapidly and asked how much discussion takes place across the centers about new data sets. Dr. Wilson noted that there is a FDA-wide working group comprised of representations across the agency who focused on next generation sequencing. CBER is taking the lead on bioinformatics on data standards.

Dr. Lein congratulated NCTR and representatives from the other FDA Centers and ORA on the remarkable integration across the centers. She has seen a huge revolution over the last three years. FDA is a complex organization with shared missions, technologies, problems and issues. She asked what structures are in place to avoid duplication. There are several forums for communications as noted by Dr. Wilson. There is an Emerging Sciences Working Group and a Senior Science Council, both constituted by senior investigators in FDA Centers and ORA. Additional groups address shared resources, identify needs for investments, etc. A MOU was signed by the Center Directors for a cost sharing model that is determined for each component. Dr. Margerrison noted that there are also many informal contacts as well. Dr. Slikker mentioned that shared funds for research (e.g., Challenge grants) bring people together as they compete for such funds. NCTR tries to disseminate their expertise to the Regulatory Centers and have biosketches of the PIs online.

Dr. Slikker thanked the SAB members and the FDA representatives.

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