

**FDA National Center for Toxicological Research
Science Advisory Board Meeting
(November 8-9, 2011)**

November 8, 2011

The meeting was called to order by the Chair of the Science Advisory Board,
Cynthia A. Afshari, Ph.D., DABT, Amgen Inc.

She welcomed the following Board members:

Ronald Hines, Ph.D., Medical College of Wisconsin

John D. Baker, Ph.D., Johnson and Johnson,

Scott W. Burchiel, Ph.D., University of New Mexico Health Sciences Center

Diana Dow-Edwards, Ph.D., SUNY Downstate Medical Center

Heidi Moline, MPH, Consumer Representative

Paul B. Watkins, M.D. of the Hamner – UNC Institute for Drug Safety Sciences
joined the meeting in the afternoon.

Also present were:

Lynn Goldman, M.D. of FDA's Science Board

John Bucher, Ph.D. representing the National Toxicology Program (NTP) at the
National Institutes for Environmental Health (NIEHS):

Carmen Maher, RN representing FDA's Medical Counter Measures program in the
Office of Chief Science in the Office of the Commissioner (OC)

Representatives from FDA's Product Centers:

Thomas Colatsky, Ph.D., Center for Drug Evaluation and Research (CDER)

Patricia Richter, Ph.D., Center for Tobacco Products (CTP)

Joseph (Gene) Leclerc, Ph.D., Center for Food Safety and Applied Nutrition (CFSAN)

Robert Sprando, Ph.D., Center for Food Safety and Applied Nutrition (CFSAN)

Steven Pollack, Ph.D., Center for Devices and Radiological Health (CDRH)

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

Karen Kreuzer, Office of Regulatory Affairs

Paul Wynne, Office of Regulatory Affairs

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

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

Margaret Ann Miller, Ph.D., Designated Federal Official

Steve Foley, Ph.D., for the Director, Division of Microbiology

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

Donna Mendrick, Ph.D., Director, Division of Systems Biology

Deborah Hansen, Ph.D., Acting Director, Division of Personalized Nutrition and
Medicine

Martha Moore, Ph.D., Director, Division of Genetic and Molecular Toxicology

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

Paul Howard, Ph.D., Associate Director, Office of Scientific Coordination

The Chair opened the meeting by welcoming all Science Advisory Board (SAB) members, FDA and other government representatives, and inviting everyone in attendance to introduce themselves.

The Designated Federal Official for the Committee read a statement that confirmed no SAB Member had any financial or other conflicts of interest with any of the topics listed in the meeting agenda. All participants were instructed to preclude themselves from further participation if the discussions turned to any topic that could be considered a conflict of interest.

Next, the Director of NCTR welcomed the SAB members and Center representatives and then gave the state of the Center address. This talk included an overview of NCTR's planning process and strategic plan, a review of NCTR's key initiatives of the past year, and a review of accomplishments. NCTR's strategic plan contains three goals: 1) Advance scientific approaches and tools necessary to support public health; 2) Develop new and innovative outreach communications materials, methods, and processes that inform and engage NCTR's internal and external target audiences; and 3) Strengthen and modernize administrative management to support FDA/HHS sciencea commitment to reach out and collaboration to strengthen NCTR for the future. The strategic goals. and research accomplishments associated with Goal 1 were discussed in more depth in each of the Division Directors' presentations and by the Director in a later in the meeting.

In reviewing the progress made under Goal 2, the Director noted that NCTR efforts to improve communication focused on improvements to NCTR's web content and the hiring of an NCTR communications officer. Efforts on modernizing management involved strengthening the IT infrastructure for scientific computing. During his review of the organizational structure, the Director noted that many of NCTR's senior scientists are eligible for retirement and may be retiring in the next two to three years. As a measure of NCTR's success, the Director pointed to the development of databases that are used throughout the agency, improvements in the process for identifying compounds for study, participation in the development of agency guidance, and integration of NCTR studies with the needs of other researchers. NCTR also has a strong commitment to training, and provides training to scientists in the area of toxicology and regulatory science.

Under Goals 2 and 3, the Director noted that NCTR has continued to work collaboratively within government and with outside groups and has developed a new research collaboration with the Center for Tobacco Products, continued the research collaboration with NICHD on methylphenidate, and joined the HESI effort to develop standards and procedures for using imaging to identify preclinical biomarkers, in addition to other leadership activities in regulatory science.

As a measure of success, the Director discussed the number of scientific publications generated by NCTR researchers during the past six years. In 2011, the number of publications will be similar to or slightly more than the 163 scientific publications

generated in 2010. NCTR's 40th anniversary celebration included a Global Summit on Regulatory Science and Innovation, a reception and dinner at the Governor's Mansion, and the 40th celebration activities at the Center. The Global Summit on Regulatory Science and Innovation was hosted by the Food and Drug Administration's (FDA) Office of International Programs (OIP) and the National Center for Toxicological (NCTR) and explored the future of research as a tool for advancing regulatory science, food safety, medical technologies, and public health through a series of presentations and panel discussions. The event was well attended by international scientists, academia from several Universities in Arkansas, and NCTR and other FDA scientists. The Global Summit was followed by a gala dinner at the Governor's Mansion to celebrate the past successes of NCTR and promote a higher profile for regulatory research in the future. The following day there was an anniversary event at NCTR which included speeches by a number of elected officials from Arkansas and the signing of an historic Memorandum of Understanding between the FDA and the State of Arkansas to set up a virtual Center of Excellence for Regulatory Science. The partnership includes the University of Arkansas System, Arkansas State University, FDA/NCTR and the State of Arkansas, and will work to forward regulatory science — especially in the area of nanotechnology. The Center Director closed with a slide summarizing the NCTR budget for the last five years and noted that this year's budget is likely to be similar to that of last year and will be supplemented by monies received through collaborations with other groups.

Following this presentation, the SAB members discussion noted that there needed to be more effort 1) in determining the impact of retirement on the strategic direction of the Center and suggested that NCTR outline a strategic direction for how the vacancies which occur due to retirements can be realigned to help meet the identified future research needs; and 2) on developing metrics in addition to publications that capture the impact of NCTR research on regulatory science. One Board member noted an interest in learning more about how social media will be used to enhance the communication of scientific results.

Following this discussion, the chair of the Division of Neurotoxicology Subcommittee Site Visit Review team outlined the key recommendations of that report. The Subcommittee visited NCTR on May 26-27, 2010. The chair noted that the Division of Neurotoxicology (DNT) is responsible for characterizing neurotoxicological and neurobehavioral toxicity. The Division has impressive breadth in the areas of imaging, molecular, behavioral, and physiology-based assessments that are complementary in nature and with few exceptions DNT responded well to the recommendations made in their previous site-visit review of January 2004. The Subcommittee found that since neurotoxicity is a common adverse response to many products regulated by the FDA, the work of this division is essential to the mission of both NCTR and FDA. The Subcommittee recommended that the Division consider hiring additional support personnel to enhance overall productivity of junior members. The Subcommittee also recommended that the Division 1) seek opportunities to translate its research accomplishments into FDA's regulatory requirements; 2) develop a strategy to keep up with non-invasive, high-throughput screening methods; 3) integrate the assessment of functional mechanisms into the research projects; 4) implement steps to optimize

resource utilization; 5) focus more efforts into the identification of biomarkers; 6) encourage and facilitate interdivisional leadership, as well as leadership within disciplines; and 7) consider whether resources and effort on the peripheral nervous system and an effort into tobacco products research should be developed in the future. The chair of the Subcommittee suggested that the issue of how to foster the integration of research results into regulatory decisions might be an issue for a discussion by the full SAB. During the discussion it was noted that the interaction with CTP has involved work on addiction but this effort occurred after the Subcommittee review.

The Director of the DNT thanked the Subcommittee for their report and provided a detailed response to the seven strategic recommendations listed above as well as to some project specific recommendations. First, the Division Director noted the Subcommittee's overall statement that the Division scientists are excellent at what they do; that their choice of study compounds is relevant, that they conduct thorough and comprehensive evaluations, and that they have exhibited excellent productivity. The DNT Director noted in his response he would focus on the Division's weaknesses as described in the Subcommittee's strategic recommendations. In response to the concern that the nonhuman primate center was being funded out of the Division's budget and, thus, taking resources from other research in the Division, the Division Director clarified that this facility was supported by NCTR approved protocols, not DNT. The Division Director also reviewed strategies being used to provide more technical support to the young principal investigators.

In response to the recommendation that DNT work to foster the translation of its research into regulatory decision-making, the Division Director noted several examples of how the Division is doing this including executing an inter-center bioimaging project, developing interactions with other FDA groups to address issues surrounding the identification of biomarkers and their qualification for regulatory purposes, playing a leadership role in the HESI imaging working group and providing testimony at an FDA Advisory Committee. In addition, the Director recently learned that Agency reviewers were requesting that sponsors of new drug applications utilize specific staining procedures (e.g. the Fluoro-Jades) developed in the Division. Thus, even in the absence of formal biomarker qualifications, the regulatory community is taking advantage of the Division's research.

In response to recommendation 2, the DNT Director noted that the Division planned to continue its efforts in cell culture and in vitro blood-brain barrier models while expanding efforts on the zebrafish model and implementing neural stem cell protocols to provide higher-throughput capabilities. To enhance the integration of functional mechanisms made in recommendation 3, the DNT Director noted plans to extend the utilization microPET/CT/MRI technologies for concomitant functional and mechanistic studies in higher species. To address recommendation 4, the DNT Director noted that the recently enacted concept paper and protocol approval procedures now require time-line information and tracks progress of key Division projects. In response to recommendation 5 to place more emphasis on biomarkers, the DNT Director noted that joint efforts with the Division of Systems Toxicology to discover biomarkers of liver injury are underway

and that DNT scientists are increasing contacts with colleagues at CDER to identify preclinical models that predict those clinical adverse events that lead to product failure. In response to recommendation 6, the DNT Director listed several recent examples of the leadership shown by DNT scientists. Finally in response to recommendation 7, the DNT Director noted that the peripheral nervous system will not be a focus area for DNT unless there is a scientific reason to investigate this issue. In cases where peripheral neurotoxicity is anticipated, every effort would be made to insure that appropriate assays were incorporated into studies.

The DNT Director went on to discuss the problem with establishing priorities within the Division but felt that working within other programs will help to focus efforts for the Division; and address some of the specific concerns raised during the Subcommittee review.

The SAB discussion focused on highlighting the need to establish a system for providing technical support for young investigators and developing a plan for determining what research areas would be phased out to support the allocation of resources into new areas. The discussion went on to explore how the issue of individual variation could be addressed in the context of nicotine addiction. The DNT Director noted that the research would investigate sex differences and genetic differences in rodent models as a first step in this process.

Next, the Acting Deputy Director of the Office of Counterterrorism and Emerging Threats (OCET) provided an overview of FDA's Medical Countermeasures Initiative (MCMi) that was launched in 2010. The MCMi, which aims to streamline and enable MCM development and regulatory evaluation is based on three pillars: 1) Enhance the review process; 2) Advance MCM regulatory science; and 3) Optimize legal, regulatory, and policy approaches. MCMi is enhancing the review process by forming public health and security action teams (Action Teams) which engage in the review process with public health MCM Enterprise, develop a "Regulatory Science Plan" for each MCM project, and provide clear development pathways based on best possible science. MCMi regulatory science is being advanced by increasing FDA capacity to help address unmet regulatory science needs for highest priority MCMs and new technologies by supporting existing and new Center programs, supporting FDA interdisciplinary inter-center collaborative programs, and developing partnerships and collaborations between FDA and others. The third pillar aims to ensure that laws and regulations support preparedness and response by implementing routine mechanisms for exchange of information with Enterprise partners, making recommendations for any statutory changes required to achieve the goal of improving emergency preparedness and response, and addressing the needs of non-Federal public-health partners. OCET is implementing this plan by improving scientific infrastructure at FDA, strengthening the workforce, engaging MCMi stakeholders, fostering transparency, and establishing and sustaining a robust MCMi regulatory science program. To this end OCET is sponsoring both intramural and extramural research projects.

During the discussion, an SAB member asked how the issue of pediatric formulations was being addressed. It was noted that there is a pediatric and maternal action team working on this issue and that they are finding that some of the issues associated with pediatric administration are similar to the problems associated with medication administration in the field, e.g., dosage formulations that do not need water for administration.

Following a short break, the meeting continued with a representative from the Division of Microbiology providing an update on the research and future plans of the Division. The presenter reviewed the Division's mission: to serve a multipurpose function with specialized expertise to perform fundamental and applied research in microbiology in areas of FDA's responsibility. Current research projects in the Division involve: 1) the development of rapid technologies to detect, identify, and molecularly characterize foodborne pathogens; 2) the characterization of antimicrobial resistance and virulence mechanisms of microbial pathogens that may enter the food supply; 3) the utilization of current molecular biological approaches to monitor interactions between human intestinal microbiota, antimicrobial agents, food contaminants, food additives and probiotics; 4) studies impacting women's health; and 5) the improvement of environmental risk assessments of priority pollutants including polycyclic aromatic hydrocarbons, and human and veterinary drugs. The Division has maintained a strong publication record during the past year and has identified six strategic research initiatives 1) to broaden its relevance to FDA and expand its collaborative relationship with FDA Product Centers and ORA; 2) to conduct value-added investigations that fill research gaps in support of the FDA Office of Food's integration efforts; 3) to develop improved methods to study the interactions between the human microbiota and antimicrobial agents, food additives, dietary supplements, food contaminants, and probiotics to gain a clearer understanding of the potential health risk of exposure to the consumer; 4) to establish studies to understand interactions of FDA-regulated products containing nanomaterials with the human microbiome and immune system; 5) to integrate "omics" technology in a systems biology context to understand the environmental fate of FDA-regulated products to help improve risk assessments; and 6) to develop a molecular diagnostic microbial-surveillance laboratory to enhance the monitoring of the experimental animals used in NCTR studies.

During the discussion, an SAB member asked if the Division had models to assess immunotoxicology and the speaker noted that there was some ongoing research to investigate some aspects of the immune system but these models are not complete. It was also noted that there may be opportunities for added work on the MCMi.

Next, the Acting Director of the Division of Personalized Nutrition and Medicine presented the Division's overall goal to support FDA and NCTR by developing and implementing research strategies that account for genetic and environmental diversity and which will produce knowledge for improving individual and public health. The Division has two groups: 1) a biometry program which works on the development of new/improved statistical methods and 2) a biology program that examines gene-environment interactions using a variety of models including *in vitro*, animal, human and a genome core laboratory. The Director reviewed several current research projects in the

area of biometry, pharmacogenomics, animal studies, and stem cells; and outlined future direction of the Division as focusing more on personalized medicine, adding work in genomic area; and moving some stem-cell research toward personalized medicine. The Acting Director noted that these ideas were tempered by the fact that she was acting in the position and that it was up to the Center Director to decide how that position will be filled.

The SAB discussion focused on how the division would integrate its work into the agency's needs in personalized medicine and how to prioritize the work in this area.

A representative from the Center for Food Safety and Applied Nutrition (CFSAN) noted that the Center's mission, i.e., 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 is safe, sanitary, wholesome, and honestly labeled; and that cosmetic products are safe and properly labeled. The representative noted that the major change is that CFSAN is now being integrated into the Office of Foods in FDA's Office of the Commissioner in support of the One-Foods Program. The representative noted that the Foods Program Focus Research Areas include: 1) chemical hazards control and non-targeted capability; 2) *Salmonella* isolation, detection, and control; 3) molecular and genetic characterization of pathogens; 4) virus contamination and control; 5) pathogen recovery improvement; and 6) nanotechnology safety in foods, cosmetics, and animal pharmaceuticals. CFSAN and NCTR continue to collaborate on several research projects including investigating 20 compounds in dietary supplements. NTP has a larger effort on determining the toxicity of dietary supplements and these efforts need to continue. CFSAN is interested in the skin penetration and toxicity of nanoparticles and in determining what studies should be used to determine the toxicity.

During the discussion, it was noted that nutrition is a CFSAN-specific issue and there is an opportunity for NCTR to engage with CFSAN on this issue.

Next, a representative from the National Toxicology Program (NTP) at the National Institute of Environmental Health Sciences (NIEHS) spoke about the founding and recent changes within the NTP program. NTP is now a Division within NIEHS in recognition of its unique status including its unique mission, research program, training opportunities and capabilities, and placement within the organization. NIEHS has also replaced the Center for the Evaluation of Risks to Human Reproduction (CERHR) with the Office of Health Assessment and Translation (OHAT) and expanded its role beyond reproduction and development assessments to a broad range of human health effects including integration and translation of data from new technologies into human-health assessments. A final change at NIEHS is the expansion of the International Cooperation on Alternative Test Methods (ICATM) to welcome Korea. The representative went on to provide the SAB with updates on the Tox 21 quantitative high-through screening activities, NTP's technical report conclusions including the results of the chronic 2-year study on *aloe vera* where clear evidence of carcinogenicity was found in male and females rats, the "Report on Carcinogens," the dietary supplements and herbal emphasis, and the recent activity on new tools to advance research on complex mixtures.

The SAB chair asked how the NCTR/NTP collaboration is being extended beyond the bioassay. The NTP representative noted that NCTR has started a seminar series and that the groups were exploring other mechanisms to extend the collaboration between the two Centers in areas of mutual interest.

The meeting adjourned for lunch and open public session.
There were no speakers at the open public session.

The update from the Office of Scientific Coordination noted that this office is responsible for 1) the Interagency Agreement (IAG) with NIEHS/NTP; (2) serving as FDA's Liaison to NIEHS/NTP; (3) the NCTR/ORO Nanotechnology Core Facility; (4) the pathology contract support; (5) conducting the Toxicology Study Support of the NCTR/NTP IAG. The IAG between FDA/NCTR and NIEHS/NTP was established in 1992 to provide FDA, in a timely manner, with the comprehensive toxicology information needed to enhance regulatory decision-making and risk-management decisions. Agents are selected for research and testing by soliciting nominations from across FDA. All studies conducted under the IAG are peer-reviewed by a committee comprised of NCTR Principal Investigators, FDA and NIEHS scientists, and representatives from other federal agencies and academia. Pathology contract support provides the expertise needed to conduct pathological examinations of animals and other advanced needed to support NCTR's mission.

Next, the NCTR Director of the Nanotechnology Core Facility provided an overview of the facility. The Nanotechnology Core Facility is a joint effort between NCTR and the Office of Regulatory Affairs' (ORA) Arkansas Regional Laboratory located at Jefferson Laboratories. It is anticipated that the methods developed by researchers at NCTR will be seamlessly transferred to the ORA enforcement activities, facilitating the development of this important technology while assuring public safety. The purpose of the facility is to support research studies by 1) characterization of nanomaterial test articles; 2) detection and characterization of nanomaterial following disposition in cells and tissues; and 3) surveillance of regulated products to monitor the manufacture and presence of nanomaterials. The facility is organized into three groups: 1) Group Electron Microscopy, 2) Particle and Elemental Analysis, and Spectroscopy Group, and 3) ORA Analytical Chemistry Group. The hiring of personnel is almost complete, the equipment for conducting a wide range of analyses is in place and several toxicology studies have been initiated.

During the discussion, one SAB member recommended that NCTR post its SOPs on the FDA.gov web site so that others could benefit from the work that has been done in developing these procedures. Another SAB member asked how projects coming into the facility were being prioritized. The NCTR Director of the Nanotechnology Core Facility noted that currently no projects are being "turned away" or prioritized but provide investigators a timeframe for when the work will be completed. The CDER representative noted that reviewers need help determining the quality of studies with

nanomaterials so they can determine what information is accurate. It was suggested that NCTR could create a database of studies with a quality measure for the study.

The SAB next heard a presentation of the report on the Subcommittee review of the Nanotechnology Core Facility of the National Center for Toxicological Research (NCTR) and Office of Regulatory Affairs (ORA). The facility was reviewed August 16 and 17, 2011. The Chair of the Subcommittee noted that this Subcommittee review was different from most Subcommittee reviews which focus on the accomplishments of Divisions. Here the Subcommittee review was conducted in order to provide early advice for the Nanotechnology Core Facility's direction. Key components of the review were a determination of the leading FDA needs in the area of nanotechnology, an assessment of the organization of the facility, and an understanding of how projects are developed within the Core, a review of the current facility and staffing plan, and an understanding of ongoing and proposed research projects. While the Subcommittee heard presentations on individual studies, the feedback on those studies was given at the meeting and was not included in the report.

The chair then noted that the key FDA research needs in the area of nanomaterials to inform FDA Risk assessment decision-making should be a priority area of work. These research needs to involve:

- 1) Basic research to determine the
 - a. Relationship between the physical properties of nanomaterials and elicited biological effects
 - b. Effects of nanomaterial composition and chemical properties on biological distribution
 - c. Mechanism of interaction between nanomaterials and organisms at the molecular and tissue level
- 2) Define and standardize how nanomaterials are characterized and assessed within biological systems
- 3) Exposure detection and measurement of nanomaterials, especially migration into foodstuffs, as an example
- 4) Modeling of nanomaterial disposition in FDA regulated products
- 5) Develop strategies for risk communication
- 6) Develop regulatory definitions for nanotechnology:
 - a. Identify the limitations of current test methods in assessing the quality and safety of nanoparticle-based therapeutics: characterization, stability, content, uniformity
 - b. Develop protocols to evaluate specific products and their review categories
 - c. Build in-house scientific expertise to support review objectives
 - d. Provide value in the regulatory coordination for products containing nanomaterials
 - e. Inform reviewer decisions and recommendations
- 7) Expertise to guide prioritization of partnered NTP studies
- 8) Provide methods for cross-validation between laboratories
- 9) Ensure outreach and coordination with other government agencies

The report went on to structure a framework for meeting the agency's needs. It was noted that the Nanotechnology Core is comprised of excellent facilities, equipment, and a well-qualified staff. As organized today, the Nanotechnology Core is available for use by NCTR investigators as needed for their individual research projects. To meet the needs of the agency, the main recommendation of the Subcommittee is to change the facility from a Core Facility into a Center of Excellence (NanoCoE) with a clear mission statement and research strategy that centers on Regulatory Nanoscience. As a first step, the Center should hire a full-time leader of the facility. This leader would then assemble a steering committee which would establish the research goals for the facility. Members of the steering committee should include representatives of key stakeholders. To free up resources to work on FDA priorities the NCTR should suspend projects that do not have direct application to regulatory decision-making. The Center of Excellence model would change the facility from a passive recipient of projects to a leader in determining what research is to be conducted. All proposals would be evaluated for: a) addressing key FDA needs in nanotechnology, b) material characterization, c) suitability of biological model, and d) fit with the overall goals of the NanoCoE and regulatory relevance. This model is similar to what is done today except that nano projects that meet the identified strategic needs would be solicited by the NanoCoE Director. Further recommendation regarding the work which is conducted at the facility includes: 1) spending time in short term (one to two years) establishing and running standards and cross-laboratory comparisons; 2) establishing a leading role in determining dosimetry models for nanomaterials; and 3) establishing informatics structures for electronically tracking samples, data, and results. Finally, NCTR needs to ensure that the work done in the facility is complementary to other efforts.

The SAB discussion noted that communication about what is available at NCTR and how scientists can collaborate to get prioritized work done will be very important. The representative from CDRH noted that a complication in moving forward in this area may be that the agency has not come to agreement on the definition of nanomaterials and that it may be difficult to establish priorities within the FDA framework. The CDER representatives noted that understanding how the information on the characterization of one type of nanoparticle can be generalized to other nanoparticles within a class and whether traditional preclinical toxicity tests are adequate to assess nanomaterials is critically important. A discussion on what projects should be suspended emphasized the Subcommittee's conclusion that using extended timelines to prioritize activities was unacceptable but deciding on priority research projects for NCTR will be difficult. The SAB members voted unanimously to accept the report.

Next, the chair of the SAB provided comments on the state of pharmaceutical research. She noted that despite the large investments in basic research and much progress in improving health, there are many unmet medical needs and that academia, industry, and government are all united in working on these needs. This collaboration of effort is beneficial because the financial resources for research are limited in all sectors. She believes that NCTR has an opportunity to both participate in these collaborations and provide leadership for partnerships particularly in the area of cardiac toxicity, new

modalities for treatments, and personalized medicine in terms of genome-wide sequencing and companion diagnostics.

The discussion supported and supplemented the observations of the presentation and noted that there were opportunities for NCTR in several product-safety initiatives and in developing animal models of disease.

[The Chair adjourned the meeting for the day.](#)

November 9, 2011

The chair resumed the meeting by having representative from Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) present their Center's mission, regulatory mandate, and discuss research needs and collaborations.

The representative from the Center for Biologics Evaluation and Research (CBER) noted their mission is to ensure the safety, purity, potency, and effectiveness of biological products, including vaccines, blood and blood products, cells, tissues and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury. The representative noted that CBER regulates complex products and relies on research to enhance its regulatory decisions. Approximately, 20% of the CBER staff are "research reviewers" whose research and review activities are integrated to ensure relevance, expertise, timeliness, and usability of the research results. During the past year, CBER developed its a Strategic Plan for Research and Regulatory Science and identified five strategic goals, i.e., 1) increase the nation's preparedness to address threats as a result of bioterrorism, pandemic and emerging infectious diseases; 2) improve global public health through international collaboration including research and information sharing; 3) enhance the ability of advanced science and technology to facilitate development of safe and effective biological products; 4) ensure the safety of biological products (post-market); and 5) enhance research excellence and accountability. CBER has been providing opportunities for scientists from CBER to meet NCTR scientists to foster research collaborations.

A member of the SAB asked if CBER could provide immunological support for studies involving nanomaterials at NCTR. The CBER representative noted that this type of cross-center collaboration was being encouraged and funded within the agency. It was also noted that the NTP has utilized this mechanism in the past and it works well. In response to a question about NCTR support for reviewing therapeutic probiotics, the Center representative noted that there was a CBER/NCTR workshop to discuss the issues about these products and foster collaborations.

The representative from the Center for Drug Evaluation and Research (CDER) noted that CDER is a large and diverse organization with many research activities and needs to fulfill the common mission of promoting and protecting the public health by ensuring that

safe and effective drugs are available to Americans. A recent meeting by CDER's Science Prioritization and Review Committee identified the following priority research needs: 1) develop quantitative methods and tools for benefit/risk analysis and enhanced detection of adverse events; 2) improve risk assessment and management strategies to reinforce the safe use of drugs; 3) evaluate the linkages between product quality attributes, manufacturing processes, and product performance; 4) evaluate the effectiveness and impact of all regulatory communications to the public and other stakeholders; 5) develop and improve predictive models of safety and efficacy in humans; 6) improve clinical trial design, analysis, and conduct; and 7) enhance the ability to individualize treatments. The CDER representative went on to give several examples of research projects including those on the mechanisms of toxicity, biomarkers, clinical pharmacology, and computational drug safety.

An SAB member asked about the goal of CDER research. The CDER representative noted that CDER has been asked to conduct a wide array of work to help CDER reviewers make regulatory decisions. In terms of determining what research is needed, the CDER representative noted that providing an open line of communication is extremely important and something that continues to be a challenge.

The Director of the Division of Biochemical Toxicology presented the Division's mission: 1) to conduct fundamental and applied research designed to define the biological mechanisms of action underlying the toxicity of products regulated by the FDA; and 2) to characterize the toxicities and carcinogenic risks associated with specific chemicals of interest to the FDA in the following three research areas: NIEHS/NTP-funded studies, food safety, and epigenetic mechanisms of carcinogenesis. The Division Director went on to review the primary research studies being conducted by each of the principal investigators and noted that the Division will continue to focus on animal toxicity studies in the near future.

The Director of the Division of Systems Biology noted that the Division consists of a multi-disciplinary team of bioinformaticians, biologists, analytical chemists, applied statisticians, physical chemists, and physicists who work in an interdisciplinary fashion using innovative and routine approaches. They convert emerging science and technology into: 1) finding new translational biomarkers to improve the safety of FDA-regulated products (drugs, devices, supplements, tobacco, etc.) and detection of disease in order to advance patient care; 2) improving detection of bacteria and viruses in food, biological products and samples resulting in better screening tools and diagnostic procedures; and 3) building bioinformatic solutions and *in silico* computational models that support regulatory science. The Division Director went on to describe one example from each of the multiple approaches used to address FDA's public-health needs including genomics, proteomics, metabolomics, bio-imaging, bioinformatics, and *in silico* modeling, and how the data from multiple technology platforms are integrated for scientific application to questions that directly support the FDA mission.

The Director of NCTR next presented a talk on the challenges and opportunities for research to advance regulatory science. Recent studies have investigated the reasons why

products fail to reach the market. Using pharmaceutical products as an example, it is clear that the inability to recognize safety issues is a major cause of product failure both before and after marketing. The disconnect between the investment in basic science research and the development of products to improve health lead to the recognition that there needs to be an increased emphasis on regulatory science. Regulatory science is the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products. NCTR with its mission to 1) conduct peer-reviewed and comprehensive toxicological research to assess safety of FDA-regulated products; 2) develop new scientific approaches and methods to speed product development; 3) provide multidisciplinary training in regulatory science; and 4) foster national and international collaborations with scientists from government, academia, and industry, is uniquely positioned to support regulatory science. NCTR's regulatory science program involves 1) leadership to strengthen and support science and promote innovation at FDA; 2) mission critical applied research; 3) scientific excellence and professional development; 4) training and retention of outstanding scientists; and 5) collaboration and partnerships throughout FDA and globally.

NCTR has engaged several next-generation regulatory science initiatives to increase the predictive capacity and cost-effectiveness of regulatory safety studies and developed collaborations within government and the state of Arkansas to promote the advancement of regulatory science through research. Globalization of the supply chain for many FDA-regulated products has put further emphasis on the need to promote regulatory science. NCTR is promoting the development of regulatory science across the globe by providing training opportunities to scientists engaged in regulatory science research. NCTR has a diverse research training portfolio including postdoctoral training program through ORISE, FDA Commissioner's Fellowship Program, and a summer student-training program. To strengthen its training of foreign scientists, in 2009 NCTR established the International Scientist Exchange Program focusing on global regulatory-science capacity building with the support of FDA's Office of International Programs. This program provides opportunities for foreign regulatory scientists to visit NCTR and learn the core competencies of regulatory research, laboratory safety, study design, ethics in research, data integrity, data analysis, and bioinformatics. The program not only provides an opportunity for scientists to conduct state-of-the art research at NCTR, it fosters success by continuing the mentorship of participants after they return to their home country.

The chair next called upon the representatives from the Center for Devices and Radiological Health (CDRH) and the Center for Tobacco Products (CTP) to present their Centers' mission, regulatory mandate, and discuss research needs and collaborations.

The representative from CDRH noted that CDRH laboratory research is housed in the Office of Science and Engineering Laboratories (OSEL) and focuses on 1) determining mechanistic understanding of physical, chemical, and biological phenomena inherent in device interactions; 2) providing independent data on product performance for CDRH decision-making; and 3) providing CDRH with proactive orientation to understand where the medical device industry is headed, not where it has been. CDRH follows the reviewer- researcher model discussed by the CBER representative. Under this model

CDRH researchers review regulatory documents, conduct basic mechanistic work to enhance product safety and effectiveness, develop test methods, participate in development of consensus standards, conduct laboratory evaluations of product failures, and train CDRH regulatory staff. OSEL has several collaborative studies with NCTR especially in the area of nanomaterials, detection of brain damage, cardiac toxicity, and cell phones.

The SAB next heard from the representative for CTP. This FDA Center was formed in 2009 to implement the Family Smoking Prevention and Tobacco Control Act. This act aims to limit the negative public-health impact of tobacco products by 1) regulating the market place; 2) preventing youth tobacco use; 3) helping adults who use tobacco to quit; and 4) reducing the morbidity and mortality of those who continue to use tobacco products. To achieve these goals, CTP's Office of Science and NCTR have developed a number of research projects intended to: 1) understand addiction; 2) measure the toxicity of intrinsically toxic products; 3) validate animal models and identify surrogates for animal models for toxic endpoints that correlate with human health outcomes; and 4) develop sensitive, predictive biomarkers of effect, and determine constituents, compounds, and design features that impact toxicity and understanding the impact of changing these product variables on toxicity.

The Director for the Division of Genetic and Molecular Toxicology noted that the Division conducts fundamental and applied research and provides expertise to meet regulatory needs of FDA. Division research attempts to balance short-term research and long-term higher risk, higher pay-off projects. The Division enjoys many successful collaborations within FDA, with other governmental agencies, and with industry. The research is conducted in four thematic areas: 1) current regulatory assays; 2) chemical-specific research; 3) promising new methods and approaches; and 4) research to improve risk assessment. The Division Director spoke about the progress of one project in each of these areas.

Following these presentations, the SAB had a general discussion. One SAB member noted that safety of pharmaceuticals is a greater problem than efficacy and most safety problems are off-target events that require toxicity studies to investigate. The NCTR Director noted that toxicity assays alone will not solve the problems identified in drug attrition studies; and therefore NCTR plans to pursue an integrated system biology approach to advance regulatory science.

The public portion of the meeting concluded and the closed session began at approximately 11:00 AM.