Division of Microbiology Response to the Science Advisory Board (SAB). Subcommittee Report

The meeting for the Science Advisory Board (SAB) Subcommittee Review of the Division of Microbiology took place virtually on August 19-20, 2020. This was the first time that an NCTR SAB meeting was held virtually instead of in-person because of COVID-19 pandemic-related travel restrictions and conference policies that were in place at the FDA. We were pleased that the meeting progressed smoothly using the WebEx platform with no IT or network connection issues for all the participants. The Subcommittee was chaired by Dr. Charles Kaspar, University of Wisconsin, and co-chaired by Dr. Mary Ellen Cosenza, MEC Regulatory & Toxicology Consulting, LLC. The subject matter expert consultants on the Subcommittee were Dr. Suresh Pillai, Texas A&M University and Dr. Douglas Rhoads, University of Arkansas, Fayetteville. All FDA Product Centers and ORA were represented on the review panel. We appreciate the thorough and critical review of the Division of Microbiology research programs by the Subcommittee, with their focus on quality of science, research productivity, strengths, opportunities, relevance and integration of the Division's research in addressing the overall public health mission of FDA. In addition, they provided guidance to Division scientists on methodological approaches and emerging innovative technologies to advance the science in support of the regulatory activities of FDA in food safety, antimicrobial resistance, nanotechnology, women's health, virology, and microbiome research within the Division.

We organized the agenda for the two-day virtual meeting so that all principal investigators in the Division had the opportunity to present overviews of their key projects' research accomplishments and future research strategies, either in oral presentations or during a virtual poster session. The Division scientists in their presentations highlighted how their research is aligned with the needs of FDA Centers. The oral presentations were grouped into three thematic topics; Topic 1: Food Safety and Virology, Topic 2: Microbiome and Biological Interactions, Topic 3: Microbial Contaminants Detection. We received positive input from the Subcommittee "that the Microbiology Division research focal areas in the program are very relevant and directly applicable to the mission of FDA product safety." In addition, the Subcommittee noted in the report that the short summaries and online posters on key findings of topics on antimicrobial resistance mechanisms, effects of antimicrobials on the gastrointestinal microbiome, the risks associated with *C. difficile* multiplying in Fecal Microbial Transplant (FMT) samples, and the development of in vitro vaginal tract models "were well done with summaries of key findings presented in a concise manner".

Response to the Subcommittee Overarching Comments about the Division of Microbiology Research Program:

We agree with the Subcommittee comment that the Division "research expertise lies in the following areas: antimicrobial resistance, host-microbiome interactions, environmental biotechnology, nanotechnology, women's health, virology and *Salmonella* virulence". We also appreciate their supportive statements on our willingness for intra-Center collaborations with other NCTR Divisions and research groups, including Biochemical Toxicology, Systems Biology, Genetic & Molecular Toxicology, Neurotoxicology, Bioinformatics & Biostatistics, Nanotechnology Core and the Veterinary Services group. The Subcommittee recognized that many of the scientists are actively engaged in national and international outreach activities. The Subcommittee noted these efforts by stating that "collaborations keep the scientists and the science relevant and up to date. This was reflected in the ability of the virology group to quickly step up to provide critical support and research on the COVID pandemic."

We thank you for the encouraging comments in the report on research productivity by stating that "The Division also presented a strong publication record (about 25-30 publications a year) that included peer-reviewed publications, book chapters, symposium and workshop proceedings. Some of the data produced by this Division has been used in the development of FDA regulatory guidance". We will continue to strive to maintain a constant publication stream in leading high-impact journals in the research focal areas that significantly impact the FDA regulatory science mission.

We agree with the Subcommittee comments that the Division's future research strategies should put an enhanced focus on prioritizing research to provide the best value to meet the FDA mission, and to avoid the research staff being spread "too thin". This includes increasing engagement with colleagues from the other Centers and enhancing communication channels to target research collaborations, keeping in mind the top research priorities and core competencies of the Division. We also agree with the Subcommittee that the Division is doing a better job since the last program review on communication with FDA Product Centers. We will emphasize even more frequent interactions that can strengthen these alliances. A helpful comment by an FDA representative suggested that holding formal and informal monthly science impact seminars would facilitate scientific exchange within the Division and across FDA Product Centers. Division Scientists will participate in NCTR quarterly research presentations to FDA Product Centers and initiate periodic seminars with our FDA stakeholders to highlight the Division's research. The Subcommittee noted that "Leadership within the Division should also examine the ideal balance between Research Scientists and Support Scientists since the current makeup appears to be heavy on Research Scientists and lacking in support staff." This is excellent advice that

we are aware of and are having internal discussions on strategies to determine the need of hiring principal investigators versus support scientists to buttress the priority areas of research in the future. In addition, future hiring plans should reflect that there is the potential for high turnover, since 42% of the principal investigators are eligible for retirement within 5 years. We will continue to address these staffing issues as we have the opportunity to hire research staff, taking into consideration the current fiscal environment at NCTR. We also appreciate that the Subcommittee acknowledged the Division leadership efforts in filling the Deputy Director, Program Specialist, Management Analyst, Support Scientist and FDA staff fellow positions since the last Subcommittee review.

We agree with the Subcommittee recommendation "that scientists from the Division communicate with faculty at institutions more broadly than the current communication that is primarily with local universities/colleges. Increased visibility and interactions beyond the State of Arkansas with doctoral Universities should expand the applicant pool." We will emphasize the need for Division scientists to be more visible to graduate students and post-docs from institutions outside of Arkansas and continue to build a pipeline for recruitment. We appreciate the suggestion by the Subcommittee that another potential venue for recruitment of post-doctoral scientists that we should take advantage of is at national meetings placement services where the Division positions could be posted, and potential candidates interviewed. We appreciate the encouraging and supportive comments by the Subcommittee that "there is no doubt that the NCTR's Microbiology Division is fulfilling a national need on a variety of topics. There is significant scientific talent and the Division administration has done a very good job in attracting additional talent at all levels". We also acknowledge the concern that the Subcommittee made about the future challenges the Division, as well as other NCTR Research programs, faces in hiring top talent and support staff, as well as providing adequate facilities to support the growth of these programs. Some of these challenges are linked to difficult budgetary resource constraints; for example, providing sufficient laboratory space, research supplies, equipment and staffing for a new hire to build their research program. However, we are being proactive in our recruiting efforts. For a research microbiologist position that we are filling, we have initiated outreach to FDA Center colleagues and research university contacts, and advertised the job announcement in a microbiology society's job placement service. Our intention is to have the opportunity to evaluate the most qualified and talented microbiologists that will meet the future strategic research initiatives of the Division This hiring effort is currently ongoing. On the topic of bioinformatics, in the virtual meeting the Deputy Division Director did comment in his presentation that many bench scientists do not have the formal educational background in bioinformatics skills that are needed to deal with large datasets. We will continue to explore outsourcing efforts, collaborations with FDA

Centers and joint projects with the NCTR bioinformatics program to follow up on the suggestions made by the Subcommittee to coalesce a strategic cluster of scientists with different domain expertise that can complement each other with individual skills in bench science, computation, and modeling. We agree such approaches will help position the Division to address complex, cross-cutting issues to enhance the regulatory science mission.

We will also maintain, as the Subcommittee indicated, that Division scientists continue or increase their participation in appropriate FDA working groups in areas such as methods development, the microbiome, antibiotic-resistant microbes, nanoparticles, etc. A challenge for the Division looking to the future is balancing on-going efforts with emerging priorities as well as defining core areas of strength and emphasis to prevent over-extension across an ever-expanding list of challenges, technologies, and disciplines. It is not possible to cover all the needs of FDA and its Centers with the existing number of staff and space.

Topic 1: Food Safety and Virology

Overarching Comments We appreciate the positive comments and suggestions provided by the Subcommittee for the individual projects within the Food Safety and Virology theme. They provided encouraging comments that the research program in food safety "satisfies an agency need and makes use of multiple areas of strength within the Division; microbiological methods, *Salmonella* and antibiotic resistance." We also value their comment that "it is clear from these projects that NCTR scientists are communicating with other centers and collaborating in a number of important areas. The lead scientists have identified significant areas on which to focus and are making excellent progress. The recruitment of Dr. Azevedo and the addition of her expertise in the area of virology demonstrates "forward thinking" by NCTR administration and scientists. Food Safety and Virology contains several core disciplines of microbiology that could be stand-alone areas of research; bioinformatics, microbial virulence, and now virology". They did highlight in the report how exciting it was to see that NCTR is playing a strong role in research related to the COVID-19 pandemic, as demonstrated by ongoing projects in the Division. We appreciate those complimentary comments and will continue to develop and strengthen the virology program, while also keeping in mind that the research studies should integrate with the FDA mission. We appreciate the supportive comments on the Role of Plasmids in Increased *Salmonella* Virulence and the Virulence and Plasmid Databases projects in collaboration with CVM that include the development of analysis tools for predicting the presence of virulence genes, which is a major accomplishment. The recommendation of the Subcommittee was to conduct experiments on extending the research on the occurrence and transfer of virulence and

antibiotic resistance genes in the pre- and post-market production practices/factors and medical devices to determine if they can be potential reservoirs of plasmid harboring pathogenic bacteria. As suggested by the Subcommittee, efforts are currently being explored to use available animal resources to help in the confirmation of virulence genotypes predicted in our in vitro and in silico efforts. The Subcommittee enthusiastically endorsed the Virulence and Plasmid Database project by commenting in the report "that a tool to predict virulence and/or antimicrobial resistance will be valuable for regulatory science involving recalls, epidemiological investigations, risk assessment and pre-harvest risk factors." For the project on Method Development and Validation for Improved Detection and Isolation of *Salmonella* in Spices, we agree with the Subcommittee recommendation to not only focus on *Salmonella* in spices but to also broaden the project to screen for enteric viruses and protozoan parasites to fill an important data gap in the food safety field. These efforts may be well suited for collaborations with CFSAN, which has active programs in enteric viruses and protozoa.

Topic 2: Microbiome and Biological Interactions

Overarching Comments: The Subcommittee reviewed the ongoing research projects that evaluate the impact of xenobiotics and nanoscale materials on the microbiomes inhabiting areas of the human body contacted by the materials, i.e. anatomical sites that include the gastrointestinal tract, vagina and skin. They commented that the research objectives are a "reasonable approach to assess potential impacts of these materials but there needs to be a link between changes in [the] microbiome with established human toxicity markers; like immune dysfunction, DNA damage, etc. Alternatively, some of these materials may increase susceptibility to infection due to alteration of the normal flora and could be evaluated using animal models." We appreciate the positive and constructive comments that "overall, this section is interacting well with the other centers and collaborating in a number of important areas. There could be stronger interactions amongst the NCTR lead scientists to maximize the return on investments." We will continue to reach out to our NCTR colleagues on the Division's expertise in microbiome research and build on the interactions that we have established with the Division of Biochemical Toxicology, Division of Systems Biology and Division of Neurotoxicology. We concur with the Subcommittee review comments and assure that when conducting toxicology safety assessments, Division scientists fully understand the importance of translating the relevance of study results from methodological approaches, like in vitro culture and animal models, to human exposure scenarios.

An excellent example is the studies conducted under the interagency agreement between NCTR/FDA and NTP/NIEHS on Approaches to Assess Xenobiotics Interaction with the Gastrointestinal Tract using Animal and Non-animal Models. Division scientists have ongoing NTP projects on arsenic, BPAF, triclosan and silver nanoparticles to determine the effect of these xenobiotics on the commensal community and gut mucosa

associated host responses during perinatal and post-natal exposure. These studies involve multifaceted and systemic evaluations of xenobiotics using various modes of exposure in animals (via oral gavage, intravenous gavage or feed), as well as, non-animal models and an ex vivo human intestinal tissue model.

The initial findings of these studies have provided evidence regarding the changes in the microbiome, host immune status and intestinal permeability. The next stage of these investigations will provide direct evidence if these changes are "good or bad" using the following approaches: susceptibility to infection and metabolic diseases, long-term effects of short duration or single exposures, strong correlation between developmental toxicity and gastrointestinal tract (GI) toxicity and relevance of animal models/genetic variants for susceptibility/resistance to GI diseases. We feel that this research will assist regulatory agencies in making safety determinations when evaluating the toxicity of xenobiotics to the host and its microbiome. We also appreciate the supportive comments on the ongoing study in collaboration with CDER that is assessing the toxicity of nanocrystal drugs using similar endpoints as described above in animal and non-animal models. For the skin microbiome project, we appreciate the positive feedback by the Subcommittee and their comment that the next phases of this CDER collaborative project on the effects of nanoscale material used in sunscreen on the skin microbiome take on a more realistic exposure approach by using a complex consortia of skin microbiota that mimics the microbial ecology of the skin. Similarly, for the OWH collaborative project on preclinical safety evaluations of nanoparticles in vaginal products, we appreciate the supportive comment that the project is "producing nice results" and agree with the Subcommittee suggestion to look at a human vaginal model that is more relevant than the mouse vaginal model that is currently being used by Division scientists.

Topic 3: Microbial Contaminants Detection

Overarching Comments: We appreciate the comments made by the Subcommittee on the research areas that focus on the detection of microbial contaminants in FDA-regulated products such as tattoo inks, pharmaceutical products, foods and fecal transplant specimens. We realize based on the Subcommittee comments that "some researchers are still relying on conventional culture-based methods to characterize microbial populations while other groups are using contemporary NGS approaches". This is primarily due to the existing protocol testing requirements in FDA guidance documents that we are required to follow for regulatory science purposes. However, we totally agree with the suggestion that "it may be useful for the researchers focusing on detection of microbial contaminants to use NGS tools to understand the genetic diversity of the samples/organisms that they are studying". We thank you for the positive feedback that overall "this section is interacting well with the other centers and collaborating on a number of important areas." To amplify with examples, we are currently developing new methods in the collaboration with CDER that allow improved

detection of *Burkholderia cepacia* complex in pharmaceutical products. We are using a variety of methods including rapid flow cytometry, molecular genetics and whole genome sequencing coupled with traditional culture-based approaches to detect very low levels of *Burkholderia* bacterial cells in pharmaceutical products. Rapid and sensitive diagnostic methods to detect harmful bacteria in pharmaceutical manufacturing are important measures to prevent contamination of manufacturing equipment and final drug products. Currently, on the collaborative project with Office of Cosmetics and Colors/CFSAN on the microbial survey of tattoo inks, permanent makeups and microblading inks, Division scientists are performing a second round of a microbial survey of tattoo inks from recalled products. In addition, we have initiated a new methods-development project to investigate the prevalence of anaerobic bacteria and their identities in set of approximately 75 tattoo inks, permanent makeups and microblading inks. We appreciate the comments made by the Subcommittee that "this is very important work and appropriate for applied FDA research. With the growing tattoo industry and the global supply chains for tattoo inks, a deep understanding of the microbial contamination in these products is important. The research conducted so far has been solid and built on good scientific principles." The Subcommittee also commented that the project Establishment of Standardized Methods for Sporicidal Efficacy Assessment is a "needed research project of importance to both the food and pharmaceutical industries." We value and will follow up on their suggestion "given that bacterial spores are of interest to a variety of federal agencies, it may be of value for the NCTR Microbiology Division to build collaborations with other Federal Laboratories that also spend considerable resources to understand bacterial spore formation, persistence and inactivation."

Overall Subcommittee Recommendations of Areas to Strengthen the Division of Microbiology Research Program to Meet FDA Mission Needs

- Focus on prioritizing research projects and emphasize those that are likely to provide the most value to best meet the FDA mission.
- Enhance communication channels with colleagues from other FDA Centers and other Research Divisions at NCTR.
- Examine the proper balance between Research Scientists and Support Scientists when developing future staffing plans.
- Hiring and succession planning should be a key area of focus due to many Principal Investigators that are eligible for retirement within the next 5 years.
- Carefully balance the breadth of ongoing research and emerging priorities as well as defining core areas of strength and emphasis to prevent the potential

overextension and spreading Division resources too thin for the Division to meet the future list of challenging public health issues.

- Work to address future challenges in hiring talented research microbiologists and support staff as well as providing adequate facilities to support the growth of research programs.
- Encourage Division leadership and scientists to continue to coordinate regular meetings, both formal and informal, to facilitate communication and interactions.
- Continue to focus research expertise in antimicrobial resistance, host-microbiome interactions, *Salmonella* virulence, virology, nanotechnology, women's health and environmental biotechnology.
- Research projects focused on both traditional microbiological and genomic approaches should increasingly incorporate, as needed, next generation sequencing as part of the techniques used in the investigations.
- Sustain outreach efforts and collaborations with the Division of Bioinformatics and Biostatistics/NCTR on bioinformatic needs to evaluate large datasets generated for ongoing and future research projects.

We appreciate the time spent by the SAB Subcommittee Expert Consultants and FDA Center Representatives to provide strategic guidance and direction in evaluating the Division's research program to advance the FDA regulatory science mission. We also want to thank the NCTR Director, Deputy Director for Research, Associate Director for Regulatory Activities and members of the NCTR administrative offices for providing support, encouragement and an excellent research environment that has made it possible for Division program staff to achieve their research and scientific career goals.