The Food and Drug Administration's (FDA's) 2015 ORSI Science Symposium April 27, 2015

SPEAKER ABSTRACTS AND BIOGRAPHIES

Introductory Remarks – 8:00-8:35 AM

Speaker	**Dr. Stephen Ostroff**
Title	**FDA Acting Commissioner**
Biography	**Dr. Stephen Ostroff, M.D., is the FDA's acting commissioner of food and drugs. As the top official of the Food and Drug Administration (FDA), Dr. Ostroff is committed to strengthening programs and policies that enable the agency to carry out its mission to protect and promote the public health.** **"It's a singular honor to be given the opportunity to represent the people of the FDA who every day dedicate their work to assure safe and effective medical products, foods, and cosmetics and to mitigate the health consequences of tobacco products," says Dr. Ostroff.** **Before being named acting commissioner, Dr. Ostroff served as the FDA's chief scientist since January 2014. In this capacity, he was responsible for leading and coordinating FDA's cross-cutting scientific and public health efforts. The Office of the Chief Scientist works closely with FDA's product centers, providing strategic leadership and support for FDA's regulatory science and innovation initiatives.** **Dr. Ostroff joined FDA in 2013 as chief medical officer in the Center for Food Safety and Applied Nutrition and senior public health advisor to FDA's Office of Foods and Veterinary Medicine.** **Prior to that he served as deputy director of the National Center for Infectious Diseases at the Centers for Disease Control and Prevention (CDC), where he was also acting director of CDC's Select Agent Program. While at CDC he focused on emerging infectious diseases, food safety, and coordination of complex outbreak response. He retired from the Commissioned Corps of the U.S. Public Health Service at the rank of Rear Admiral (Assistant Surgeon General). Dr. Ostroff was also the director of the Bureau of Epidemiology and acting physician general for the Commonwealth of Pennsylvania and has consulted internationally on public health projects in South Asia and Latin America.** **Dr. Ostroff graduated from the University of Pennsylvania School of Medicine in 1981 and completed residencies in internal medicine at the University of Colorado Health Sciences Center and preventive medicine at CDC.**

Speaker	**Dr. Carol Linden**
Title	**Director, Office of Regulatory Science & Innovation**
Biography	**Dr. Linden currently serves as the Director, Office of Regulatory Science and Innovation in the Office of the Chief Scientist, Office of the Commissioner, U.S. Food and Drug Administration. There she oversees a broad array of both intramural and extramural programs focused on bringing understanding of the latest in scientific and technological advances to the process of regulating products that support the health of the American public. Prior to assuming this position, Dr. Linden was the Principal Deputy Director of the Office of the Biomedical Advanced Research and Development Authority (BARDA) in the Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services. Her duties included oversight of advanced development and acquisition programs for Project BioShield medical countermeasures for CBRN threats as well as pandemic influenza vaccines, drugs, diagnostics and infrastructure. From October 2006 through April 2008 she also served as the Acting Director of BARDA, responsible for a doubling in the size of the office and implementation of the legislation that established the office.** **In 2009, Dr. Linden co-chaired with the Department of Defense the Working Group on Strengthening the Biosecurity of the United States, which was mandated by an Executive Order, and produced a report with recommendations submitted to the White House. She also played an active role in the Trans-Federal Task Force on Optimizing Biosafety and Biocontainment Oversight, which made recommendations to support improvements in eight areas. More recently, she provided expertise to the Federal Experts Security Advisory Panel under the Executive Order "Optimizing the Security of Biological Select Agents and Toxins in the United States, and co-chaired a 2014 working group under the FESAP to review opportunities for improvements to the Select Agent Program.** **Dr. Linden previously served as the Senior Scientist for the Office of Research and Development in the Science and Technology Directorate of the Department of Homeland Security, overseeing treaty and regulatory compliance as well as international collaborations. Immediately prior to this position, she served as Deputy Director of the Office of Research Programs. Prior to joining the Department of Homeland Security, Dr. Linden was the Scientific Director for the Defense Threat Reduction Agency (DTRA) Chemical and Biological Defense Directorate from mid-2003 until spring of 2004. Before her detail to DTRA, she served as the Director for the Department of Defense Medical Chemical and Biological Defense Research Programs for over 3 years, managing all aspects of the joint services medical Chemical and Biological Defense Program. Dr. Linden served a critical function in coordinating the working relationship between the technology base and advanced development, facilitating the transition of candidate vaccines, diagnostic technologies and therapies to the developer.** **Dr. Linden obtained her bachelor's degree in biology from Bryn Mawr College, and a Ph.D. from the University of California Los Angeles in molecular biology. She conducted postdoctoral research at the California Institute of Technology and University of Maryland prior to joining the research staff at the U.S. Army Medical Research Institute of Infectious Diseases, where she subsequently served as the Chief, Research Plans and Programs.**

Speaker	**Dr. Frank Weichold**
Title	**Director, Critical Path and Regulatory Science Initiatives**
Biography	**Dr. Weichold is director for the Office of Critical Path and Regulatory Science Initiatives in the office of the Chief Scientist and the Office of the Commissioner for the Food and Drug Administration. He also chairs the FDA Senior Science Council and he represents FDA at the Maryland Life Science Advisory Board. The expertise he brings to the regulatory agency builds on his ability to advance, coordinate, and integrate scientific resources for FDA by addressing mission critical scientific regulatory challenges in a global environment. The FDA Centers of Excellence in Regulatory Science and Innovation (CERSI) network is being built under Dr. Weichold's leadership in collaboration with academic institutions to leverage scientific expertise, resources and capacity toward FDA's mission. He is leading strategic partnership arrangement and value generation at the agency, including intellectual property development and technology transfer.** **Dr. Weichold's experience includes execution of strategic and operational initiatives across the sciences' value chain. Dr. Weichold has led the development of international collaborations and public private partnerships for discovery and early medical product development, implemented global operating and development models, and executed large-scale business model transformations. He has accumulated more than a decade of industrial research and medical product development experience while leading teams in Clinical Pharmacology, DMPK, as a Director at MedImmune LLC, and AstraZeneca. Prior, he directed research and clinical development of vaccines at the Aeras Foundation (founded by The Bill and Melinda Gates Foundation).** **As a tenured Professor in the University of Maryland system, he developed and managed independent research programs and trained graduate students. He also held faculty positions at the University of Maryland Biotechnology Institute to study signal transduction pathways that affect immune responses, as well as at the Humboldt University, Berlin (Germany) to teach and study microbial immune modulation. During the five years of postdoctoral education, Dr. Weichold worked at the National Institutes of Health in Bethesda, Maryland, first at the National Cancer Institute where he researched immune pathologies in HIV infection, then at the Hematology Branch of the National Heart Lung and Blood Institute where bone marrow pathologies, transplantation immunology and gene therapy were the focus of his clinical research studies. His medical practice and clinical experience include Infectious Diseases and Immunology/Rheumatology.**

Speaker	**Dr. Taha Kass-Hout**
Title	**FDA Chief Health Informatics Officer, CTO, and Director, Office of Informatics and Technology**
Biography	**Taha Kass-Hout has been a leader in the fields of health and informatics for nearly two decades. He is the first Chief Health Informatics Officer of the US Food and Drug Administration (FDA). A believer in open government, Kass-Hout is an advocate for innovation and public-private partnership and collaboration evident by his creation of openFDA. In alignment with the White House Cloud Initiative, Kass-Hout launched the first Department of Health and Human Services program to be completely hosted in the cloud in 2009. In 2012, he was co-chair of the White House Office of Science and Technology Policy (OSTP) Biosurveillance sub-committee, charged with "detecting aberrations from the norm." Through his leadership in information management, Kass-Hout has frequently been involved in the response to global disease outbreaks. In 2003, with the outbreak of SARS, he helped to develop the eQuest data collection and analysis platform for the Centers for Disease Control and Prevention (CDC). In 2009-2010, he supported CDC as it called for hospital emergency department monitoring in coordination with local, state and federal public health agencies during the H1N1 pandemic.** **Kass-Hout is credited with a number of humanitarian innovations. In 2010, for example, the Thomson Reuters Foundation used the InSTEDD Riff open source social networking platform he co-developed to communicate with survivors of the earthquake in Haiti. Free text messages sent to mobile phones allowed the people of Port Au Prince to receive the latest disaster-relief information. Kass-Hout earned a master of science degree from the Department of Biostatistics at the University of Texas School of Public Health. His MD degree is from the University of Texas Health Sciences Center in Houston, where he also completed some of his clinical training. Additional training was accrued at Beth Israel Deaconess Medical Center, which is affiliated with Harvard University.**

University of Maryland CERSI

CERSI	**University of Maryland**
Speaker	**William E. Bentley, PhD**
Title and Location	**Robert E. Fischell Distinguished Professor & Chair** **Fischell Department of Bioengineering** **University of Maryland, College Park, MD**
Biography	**William E. Bentley is the Robert E. Fischell Distinguished Professor of Bioengineering and founding Chair of the Fischell Department of Bioengineering at the University of Maryland. His B.S. and M.Eng. degrees were from Cornell University; his Ph.D. from the University of Colorado. All were in chemical engineering. At Maryland since 1989, Dr. Bentley research has focused on the expression of biologically active proteins, deciphering and manipulating cell-cell communication pathways, and connecting microfabricated devices with biological systems via "biofabricated" interfaces. He has authored over 250 archival publications and mentored 33 PhDs and 22 postdocs. He is co-PI of Maryland's Center of Excellence in Regulatory Science and Innovation (CERSI), a joint initiative with the FDA. He is co-PI of the National Capital Consortium for Pediatric Device Innovation (www.innovate4kids.org), funded by the FDA's Office of Orphan Products Development. Dr. Bentley was recipient of the Charles Thom Award of the SIMB, the AIChE's FPB Division Award, and the ACS BIOT Division's Marvin Johnson Award. He is also a Fellow of the ACS, AAAS, and AIMBE and is an elected member of the American Academy of Microbiology.**
Presentation Title	**Science that speeds health innovation**
Presentation Abstract	**The UM-CERSI advances regulatory science by providing: 1) direct scientific and training linkages between the FDA and the two leading UM campus; and 2) cutting edge regulatory science research experiences for teams of FDA and UM personnel in collaborative research projects. These projects have been diverse, reflecting the breadth of expertise at UMB and UMCP. They range from studies of "Antipsychotic drug use in nursing home (NH) elders with dementia", to "Development of Standards for the Evaluation of Conventional and Advanced Tissue Engineering Scaffolds," and "Best practices for transporter in vitro assays", to name a few. To-date, several validated standard methods have been developed and 18 research papers have been published in top tier scientific journals.** **The UM-CERSI Center-wide activities that promote regulatory science within the broader scientific community have also been tremendously successful. For example, to-date 1,895 FDA scientists and engineers have attended UM-CERSI seminars held monthly at the White Oak campus; 3,110 individuals from across the spectrum (FDA, academia, and industry) have attended the CERSI-sponsored workshops. Topics have also varied significantly, a few being: "Top Down Analysis of Antibodies", "Patient Focused Drug Development", and "AIMBE/NIH Workshop on Validation and Qualification of New In Vitro Tools and Models for the Pre-Clinical Drug Discovery Process". Finally, the UM-CERSI has started an MS program (> 50 students enrolled) within Pharmacy at UMB and an MEng Certificate (>20 enrolled) within Bioengineering at UMCP aimed primarily at practitioners seeking additional education and training in their career development.**

CERSI	**University of Maryland**
Speaker	**Yu Chen, PhD** **Associate Professor** **University of Maryland, College Park, MD**
Title and Location	**Yu Chen, PhD**
Biography	**Dr. Yu Chen is an Associate Professor of Bioengineering at the University of Maryland, College Park, USA. Dr. Chen received his B.S. degree in Physics from Peking University in 1997, and his Ph.D. degree in Bioengineering from University of Pennsylvania in 2003. Dr. Chen's research interests encompass the areas of biomedical photonics and imaging, including optical coherence tomography (OCT), multiphoton microscopy (MPM), needle-based endoscopy, and biomedical applications such as kidney imaging, brain mapping, and cancer detection. He has Jed numerous research projects funded by NIH and NSF. He has published more than 60 peer-reviewed papers. Dr. Chen is a Fellow of the American Society for Laser Medicine and Surgery.**
Presentation Title	**3D Printed Biomimetic Phantoms for Assessment of Biophotoinics Imaging Systems**
Presentation Abstract	**The emerging technique of three-dimensional (3D) printing provides a revolutionary way to fabricate objects with biologically realistic geometries. We have performed optical and morphological characterization of basic 3D printed tissue-simulating phantoms and found them suitable for use in evaluating biophotonic imaging systems. We also assess the potential for printing** **phantoms with irregular, image-defined vascular networks that can be used to provide clinically-relevant insights into device performance. A polymer with biologically realistic optical properties was identified by spectrophotometer measurements of several commercially available samples. Phantoms were printed with the retinal vascular network reproduced as~ 1.0 mm diameter channels at a range of depths up to~ 3 mm. The morphology of the printed vessels was verified by volumetric imaging with µ-CT. Channels were filled with hemoglobin solutions at controlled oxygenation levels, and the phantoms were imaged by a near-infrared hyperspectral reflectance imaging (HRI) system. Overall, results indicated that 30 printed phantoms are useful for assessing biophotonic system performance and have the potential to form the basis of clinically-relevant standardized test methods for assessment of medical imaging modalities.**

CERSI	**University of Maryland**
Speaker	**Bruce Yu, PhD**
Title and Location	**Associate Professor of Pharmaceutical Sciences** **University of Maryland, Baltimore, MD**
Biography	**Dr. Yu received his B.S. in biochemistry from Peking University and Ph.D. in biophysics from the Johns Hopkins University. His postdoctoral training was in NMR spectroscopy at SUNY Buffalo and peptide chemistry at the University of Alberta. In his independent research career at the at the University of Utah and at the University of Maryland, Dr. Yu has worked on developing magnetic resonance imaging agents and biomaterials . His current research interest is to develop noninvasive chemical analysis using NMR for product inspection, especially for pharmaceutical solutions. Dr. Yu received the Kimmel Scholar Award in 2004 and the Presidential Early Career Awards for Scientists for Engineers in 2005.**
Presentation Title	**Noninvasive Detection of Protein Aggregation using Water Proton NMR**
Presentation Abstract	**Protein drugs have a tendency for from harmful aggregates in solutions. Such aggregation can occur in finished drug products due to various physical stresses, such as agitation and heating, commonly encountered transportation and storage. Currently, once a protein drug vial if filled and sealed, only visual inspection is possible. This is because existing aggregation detection techniques are invasive; they require opening the drug vial and drawing out a portion of the drug solution for analysis.** **Giving aggregated protein drugs to patients is avoidable if the aggregation level in each vial is assessed right before injection. This requires a simple noninvasive aggregation detection technique.** **In this presentation, we report such a technique based on the water proton NMR signal. Aggregation detection is conducted non-invasively by putting an unopened vial of protein solution into a low-field benchtop NMR spectrometer. Because water is the solvent of every biopharmaceutical solution, this technique has wide applicability. The measurement process is simple and fast.**

Johns Hopkins University CERSI

CERSI	**Johns Hopkins University**
Speaker	**G Caleb Alexander, MD, MS**
Title and Location	**Co-Director, Johns Hopkins Center for Drug Safety and Effectiveness** **Associate Professor, Epidemiology and Medicine** **Johns Hopkins Bloomberg School of Public Health** **Department of Epidemiology** **Baltimore, MD**
Biography	**G. Caleb Alexander, MD, MS is an Associate Professor of Epidemiology and Medicine at Johns Hopkins Bloomberg School of Public Health, where he serves as a founding co-Director of the Center for Drug Safety and Effectiveness. He is a practicing general internist and pharmacoepidemiologist and is internationally recognized for his research examining prescription drug utilization. Dr. Alexander is the author of over 170 scientific articles and book chapters, and he has published regularly in leading scientific journals including JAMA, Health Affairs and the Annals of Internal Medicine. He is a frequent speaker on health care issues and has served on numerous editorial and advisory boards, including Drug Safety, Journal of General Internal Medicine, American Journal of Health System Pharmacy, Medical Decision Making and Medical Care. Due to its impact and relevance to a broad sector of the general public, his work has been widely featured in a media including the Economist, Scientific American, the New York Times, the Wall Street Journal, Washington Post, National Public Radio and other media. Dr. Alexander's research focuses on population-based patterns and determinants of pharmaceutical use, clinical decision-making regarding prescription drugs, and the impact of changes in regulatory and payment policy on pharmaceutical utilization. In addition to expertise conducting survey-based investigations, he has also extensive experience with the analysis of secondary data sources including administrative claims and large national surveys. Dr. Alexander received his B.A. cum laude from the University of Pennsylvania, an MD from Case Western Reserve University, and a Master of Science from the University of Chicago.**
Presentation Title	**Regulatory Science and Innovation: Optimizing the Evidentiary Basis for Decision-Making at the FDA**
Presentation Abstract	**The Johns Hopkins University (JHU) Center of Excellence in Regulatory Science and Innovation (CERSI) builds on the enormous strengths of Johns Hopkins University in quantitative sciences and pharmacology to provide novel education, exchange and collaborative research programs that are focused on three specific areas of FDA's regulatory science and innovation strategy which include: (i) Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development; (ii) Ensure FDA Readiness to Evaluate Innovative Emerging Technologies; and (iii) Harness Diverse Data through Information Sciences to Improve Health Outcomes. In his brief remarks, Dr. Alexander will describe the key features of the JHU CERSI and highlight the research projects and educational programs underway during its first year of collaboration with the FDA.**

CERSI	**Johns Hopkins University**
Speaker	**John Bridges, PhD**
Title and Location	**Associate Professor of Health Policy and Management, Health, Behavior and Society, International Health, Johns Hopkins Bloomberg School of Public Health; Baltimore, MD**
Biography	**John F P Bridges PhD is an international leader in the application of stated-preference methods. He is the founding editor of The Patient – Patient Centered Outcomes Research and has worked with numerous patient groups, health technology assessment agencies, regulators and international aid agencies to advance and apply these methods to document the preferences of patients and other stakeholders. Within the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) he founded the Conjoint Analysis Working Group (2006-2011), the Conjoint Analysis Task Force (2008-2010) and was the first author on the ISPOR checklist conjoint analysis. In 2006 he received ISPOR's Bernie O'Brien New Investigator Award and in 2011 received an ISPOR Distinguished Service Award for his leadership of conjoint analysis methods. He is the author of over 100 publications and a frequent speaker on patient engagement, patient preferences and benefit-risk analysis. John is an associate professor in the Department of Health Policy & Management, where he serves as the Director of the Masters of Health Science (MHS) in Health Economics, and has joint appointments in the Department of International Health and Department of Health Behavior and Society. He is core faculty within the Center for Health Services and Outcomes Research (CHSOR), the Center for Drug Safety & Effectiveness (CDSE), and the Center for Excellence in Regulatory Science and Innovation (CERSI). He is also a Faculty Research Fellow at the National Bureau of Economic Research (NBER) and a Senior Fellow at the Center for Medicine in the Public Interest (CMPI).**
Presentation Title	**Partnership to advance stated-preferences methods in regulatory science**
Presentation Abstract	**This project builds off a PCORI funded project at Johns Hopkins that advances and applies stated-preferences among people with type 2 diabetes. As a PCORI methods project, we aimed to address several research gaps pertaining to patient and community engagement and to the application of stated-preference methods to measure the priorities and preferences of patients and other stakeholders. This work parallels FDA efforts to identify and apply approaches and methods to better engage patients and caregivers in the regulatory process and to identity methods to inform regulatory benefit-risk decisions. This CERSI project aims will offer an important mechanism for communication and collaboration between the FDA and Johns Hopkins collaborators to share, review, and implement knowledge about stated-preference methods.** **This collaboration presents a significant opportunity to build synergies between existing FDA and Johns Hopkins projects. It builds off a sizable methods project funded by PCORI that will fund the development, implementation and dissemination of two important experiments. The first experiment compares traditional rating/ranking approaches to measuring priorities of people with type 2 diabetes (focused on barriers and facilitators to self-management) with innovative best-worst scaling methods. The second experiment compares traditional conjoint analysis/discrete-choice experiments approaches to innovative best-worst scaling methods to measure the treatment preferences of people with type 2 diabetes. These two experiments-of-experiments will provide important information about the comparability of various stated-preference methods and will provide a vehicle for disseminating these methods.** **In addition to simple comparisons of these two methods, this PCORI study also aims to compare two approaches for studying preference heterogeneity. The first approach is traditional stratification, where the preferences of different groups (including groups defined on clinical and demographic characteristics) are compared and tested. To facilitate this stratification, we plan to oversample base on race and ethnicity. The second approach, segmentation, uses techniques such as latent class analysis to identify groups with similar preferences. Differences in clinical and demographic characteristics of these groups can then be compared using traditional epidemiological methods. The study of preference heterogeneity is relevant to the FDA as a means to study difference in risk tolerance in difference subgroups of patients.**

Georgetown University CERSI

CERSI	**Georgetown University**
Speaker	**Ira Shoulson, MD**
Title and Location	**Professor of Neurology, Pharmacology, and Human Science** **Director, Program for Regulatory Science & Medicine** **Principal Investigator, Center of Excellence in Regulatory Science and Innovation (CERSI)** **Georgetown University, Washington, DC**
Biography	**Ira Shoulson, MD, is Professor of Neurology, Pharmacology, and Human Science, and Director of the Program for Regulatory Science and Medicine (PRSM) [http://regulatoryscience.georgetown.edu] at Georgetown University, Washington, DC. From 1990 until 2011, Dr. Shoulson was the Louis C. Lasagna Professor of Experimental Therapeutics and Professor of Neurology, Pharmacology and Medicine at the University of Rochester School of Medicine & Dentistry in Rochester, New York, where he currently holds adjunct appointments as Professor of Neurology, Pharmacology & Physiology. He received his MD degree (1971) and postdoctoral training in medicine (1971-73) and neurology (1975-77) at the University of Rochester and in experimental therapeutics at the National Institutes of Health (1973-75). Dr. Shoulson founded the Parkinson Study Group (www.parkinson-strudy-group.org) in 1985 and the Huntington Study Group (www.huntington-study-group.org) in 1994 -- international academic consortia devoted to research and development of treatments for Parkinson disease, Huntington disease, and related neurodegenerative and neurogenetic disorders. He was a key investigator in the US-Venezuela Collaborative Huntington Disease Project, which identified the gene responsible for this fatal hereditary disorder. Dr. Shoulson has served as principal investigator of the National Institutes of Health-sponsored trials, "Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism" (DATATOP), the "Prospective Huntington At Risk Observational Study" (PHAROS), and in the leadership of more than 35 other multi-center clinical research studies. He played an instrumental role in the development of 10 new drugs for neurological disorders, including seven for Parkinson disease (selegiline, lazabemide, pramipexole, entacapone, clozapine, rasagiline, rotigitine), two for Huntington disease (tetrabenazine, dutetetrabenazine), and one for attention deficit disorder (Concerta). He was formerly a health policy fellow in the U.S. Senate, a member of the National Institute of Neurological Disorders and Stroke Council, and president of the American Society for Experimental NeuroTherapeutics (ASENT). He is currently principal investigator of the FDA-Georgetown University Collaborating Center of Excellence in Regulatory Science and Innovation (CERSI - FD004319), associate editor of JAMA Neurology and an active elected member of the Institute of Medicine of the National Academy of Sciences. He has authored more than 300 scientific reports.**
Presentation Title	**Overcoming Challenges to Medical Product Innovation**
Presentation Abstract	**Georgetown University Center of Excellence in Regulatory Science and Innovation (CERSI) promotes and supports collaborative approaches to address current and emerging regulatory science decision-making challenges. Success of these efforts has been demonstrated through tangible value created in regulatory science research, education and training, and scientific exchange. In his brief remarks, Ira Shoulson, MD, will describe the key features of the Georgetown CERSI and highlight milestones achieved in the first four years of collaboration with the FDA.**

CERSI	**Georgetown University**
Speaker	**Peter McGarvey, PhD**
Title and Location	**Research Associate Professor** **Innovation Center for Biomedical Informatics** **Department of Biochemistry and Molecular & Cellular Biology** **Georgetown University, Washington, DC**
Biography	**Dr. Peter McGarvey is Research Associate Professor, Department of Biochemistry and Molecular & Cellular Biology, Georgetown University Medical Center (GUMC). Has academic and commercial experience in molecular biology, biotechnology, bioinformatics and software development, and his research interests include genomic and proteomic analysis, biological databases, and data visualization. Currently, Dr. McGarvey helps manage several projects at ICBI and GUMC including the CPTAC Data Center, Georgetown University Center of Excellence in Regulatory Science and Innovation (CERSI), bioinformatics component of the Georgetown-Howard University CTSA, Protein Information Resource, and UniProt Knowledgebase. Dr. McGarvey has a PhD in Biological Sciences from the University of Michigan and an MS in Technology Management from University of Maryland University College.**
Presentation Title	**Genetics of Vaccine Safety Signal Detection: Supporting FDA's Data Mission Through Informatics**
Presentation Abstract	Near universal administration of vaccines mandates intense pharmacovigilance for vaccine safety and a stringently low tolerance for adverse events. Reports of autoimmune diseases (AID) following vaccination have been challenging to evaluate given the high rates of vaccination, background incidence of autoimmunity, and low incidence and variable times for onset of AID after vaccinations. To identify biologically plausible pathways to adverse autoimmune events of vaccine-related AID, we used a systems biology approach to create a matrix of innate and adaptive immune mechanisms active in specific diseases, responses to vaccine antigens, adjuvants, preservatives and stabilizers, for the most common vaccine-associated AID found in the Vaccine Adverse Event Reporting System. **Results:** This report focuses on Guillain-Barre Syndrome (GBS), Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), and Idiopathic (or immune) Thrombocytopenic Purpura (ITP). Multiple curated databases and automated text mining of PubMed literature identified 667 genes associated with RA, 448 with SLE, 49 with ITP and 73 with GBS. While all data sources provided valuable and unique gene associations, text mining using natural language processing (NLP) algorithms provided the most information but required curation to remove incorrect associations. Six genes were associated with all four AIDs. Thirty-three pathways were shared by the four AIDs. Classification of genes into twelve immune system related categories identified more "Th17 T-cell subtype" genes in RA than the other AIDs, and more "Chemokine plus Receptors" genes associated with RA than SLE. Gene networks were visualized and clustered into interconnected modules with specific gene clusters for each AID, including one in RA with ten C-X-C motif chemokines. The intersection of genes associated with GBS, GBS peptide auto-antigens, influenza A infection, and influenza vaccination created a subnetwork of genes that inferred a possible role for the MAPK signaling pathway in influenza vaccine related GBS. **Conclusions:** Results showing unique and common gene sets, pathways, immune system categories and functional clusters of genes in four autoimmune diseases suggest it is possible to develop molecular classifications of autoimmune and inflammatory events. Combining this information with cellular and other disease responses should greatly aid in the assessment of potential immune-mediated adverse events following vaccination.

University of California-San Francisco/Stanford University CERSI

CERSI	**University of California-San Francisco (UCSF)-Stanford University**
Speaker	**Russ B. Altman, MD, PhD**
Title and Location	**Professor and Co-Director** **UCSF-Stanford CERSI** **Departments of Bioengineering, Genetics, Medicine and Computer Science** **Stanford University, Stanford, CA**
Biography	**Russ Biagio Altman is a professor of bioengineering, genetics, & medicine (and of computer science, by courtesy) and past chairman of the Bioengineering Department at Stanford University. His primary research interests are in the application of computing and informatics technologies to problems relevant to medicine. He is particularly interested in methods for understanding drug action at molecular, cellular, organism and population levels. His lab studies how human genetic variation impacts drug response (e.g. http://www.pharmgkb.org/). Other work focuses on the analysis of biological molecules to understand the action, interaction and adverse events of drugs (http://features.stanford.edu/). He has chaired the Science Board advising the FDA Commissioner. He currently serves on the Advisory Committee to the NIH Director.**
Presentation Title	**UCSF-Stanford Innovative Regulatory Science on the West Coast**
Presentation Abstract	**Research Projects Overview:** 5 research projects have been funded so far this year which involve teams of FDA and UCSF/Stanford scientists working on areas of research that are critical for approval of medical products. These include projects focused on: • **Improving Pharmacovigilance (two projects)** Nigam Shah will present the initial progress on: "Improving ADR Signal Detection by Combining Signals from Spontaneous Reports and Electronic Health Records". • **Developing In Vitro Methods to Inform the Conduct of Clinical Studies in Patients with Drug-induced Renal Impairment.** Kathy Giacomini will present initial progress on: "Renal Impairment in New Drug Development" and in the afternoon of the Science Symposium UCSF postdoc; Chia-Hsiang Hseuh will give a poster presentation. • **Developing Standards for Spinal Devices** • **Developing Standardized Data Formats for the Electronic Health Record to Enhance the Conduct of Clinical Trials** **Educational Programs Overview:** the CERSI educational team is in the process of designing and implementing CERSI educational programs in Regulatory Sciences, which will focus especially on regulatory sciences of special interest to west coast industries. We plan to roll out an exciting curriculum at UCSF and Stanford that will be available not only to students, postdocs and faculty at UCSF and Stanford, but to industry and FDA scientists as well. Professional Certificate Programs on Fundamentals and Frontiers in Regulatory Science in development.

CERSI	**University of California-San Francisco (UCSF)-Stanford University**
Speaker	**Kathy M. Giacomini, PhD**
Title and Location	**Professor and Co-Director** **UCSF-Stanford CERSI** **Department of Bioengineering and Therapeutic Sciences** **University of California, San Francisco, CA**
Biography	**Dr. Kathy Giacomini received her Ph.D. in Pharmaceutics from the State University of New York at Buffalo and completed a post-doctoral fellowship at Stanford University. Dr. Giacomini is considered a leader in the field of pharmacogenomics of membrane transporters. She led the discovery of coding region variants of about 50 membrane transporters that play a role in drug response in ethnically diverse populations. Dr. Giacomini and her group functionally characterized over 100 transporter variants in cells, discovering both gain of function and loss of function variants that may lead to variation in drug response. She has received numerous awards for her research including the Dawson Award of the American Association of Colleges of Pharmacy; the Research Achievement Award in Drug Metabolism from the American Association of Pharmaceutical Scientists and the Rawls Palmer Award from the American Society for Clinical Pharmacology and Therapeutics. She is an elected member of the National Institute of Medicine.**
Presentation Title	**Renal Impairment in New Drug Development**
Presentation Abstract	**Organic anion-transporting polypeptide 1B1 (OATP1B1) and organic anion-transporting polypeptide 1B3 (OATP1B3) are two major hepatic transporters which play important roles in drug elimination. This presentation details our investigation on whether uremic toxins, which accumulate in renal impairment, inhibit the activities of these two transporters. At around 100x free uremic concentration, creatinine, indoxyl sulfate, and p-cresyl sulfate resulted in OATP1B1 inhibition rates of 38%, 53%, and 31%, respectively. Incubation with homocysteine and indoxyl sulfate resulted in OATP1B3 79% and 33% inhibition, respectively. IC50 of indoxyl sulfate was 2232±61uM for OATP1B1 and 1077±67uM for OATP1B3. Homocysteine inhibited OATP1B3 at an IC50 of 1108±53uM. In conclusion, we have identified several uremic toxins that inhibit OATP1B1 and OATP1B3. Notably, indoxyl sulfate is a mutual inhibitor of OATP1B1 and OATP1B3, and homocysteine potently inhibits OATP1B3. Furthermore, treatment with a cocktail of uremic toxins displayed an increased inhibitory effect. These results suggest that the accumulation of uremic toxins observed in renal impairment functions to inhibits the activity of OATP1B1/1B3, which leads to altered pharmacokinetics for certain drugs as observed clinically.**

CERSI	**University of California-San Francisco (UCSF)-Stanford University**
Speaker	**Nigam H. Shah, MBBS, PhD**
Title and Location	**Assistant Professor** **Medicine (Biomedical Informatics)** **Stanford University, Stanford, CA**
Biography	**Dr. Nigam Shah is assistant professor of Medicine (Biomedical Informatics) at Stanford University, Assistant Director of the Center for Biomedical Informatics Research, and a core member of the Biomedical Informatics Graduate Program. Dr. Shah's research focuses on combining machine learning, text-mining, and prior knowledge in medical ontologies to enable use cases of the learning health system.** **Dr. Shah received the AMIA New Investigator Award for 2013. Dr. Shah integrates teaching into his advanced research work and was recognized with the Biosciences Faculty Teaching Award for outstanding teaching contributions in his graduate class on "Data driven medicine" (Biomedin 215). He holds an MBBS from Baroda Medical College, India, a PhD from Penn State University and completed postdoctoral training at Stanford University. More at: https://med.stanford.edu/profiles/nigam-shah**
Presentation Title	**Improving ADR Signal Detection by Combining Signals from Spontaneous Reports and Electronic Health Records**
Presentation Abstract	**Adverse drug events (ADEs) are undesired harmful effects resulting from use of a medication, and occur in 30% of hospitalized patients. We propose to augment ADR signal detection by combining datasets that capture complimentary dimensions about drug safety profiles.** **Our approach has two parts: 1) We characterize the relative gain in signal detection accuracy by combining FAERS and EMR data instead of using them in isolation. 2) We then build a machine learning system that operates on EMR data, and alerts clinicians to situations where submission of a FAERS report should be considered. In this presentation, we will review initial results on the machine learning system, which uses the text from 9.5 million clinical notes, along with prior knowledge of drug usages and known adverse drug events, as inputs. These inputs are used by a discriminative classifier which outputs the probability that a given drug-disorder pair represents a valid adverse drug event association. We evaluate our method by assessing support for the predictions in other curated data sources, including a manually curated, time indexed reference standard of label change events. Our classifier achieves an area under the curve (AUC) of 0.94 on a held out test set, and predicts 240 high-confidence, well-supported drug-AE associations. 36% of the predictions are supported in at least one of the resources which have information that was not available to the classifier; demonstrating the feasibility of systematic post-marketing surveillance for ADEs using machine learning electronic medical records.**

Session 4: Broad Agency Announcement (BAA) Research Contract Program Presentations – 1:45-3:00 PM

Speaker name and title	**Bill Murray, President and CEO of Medical Device Innovation Consortium (MDIC)**
Contractor	**Medical Device Innovation Consortium (MDIC)**
Biography	**Bill joined MDIC in August of 2013 as the first President and CEO. He has over 25 years of senior leadership experience spanning the range of privately financed start-up to billion dollar plus global businesses. Bill's small company experience spans 5 years as CEO and executive consultant, including 3 years as CEO of ReShape Medical. His large company experience includes leadership as the Molecular Biology Division President of Applied Biosystems, and at Medtronic where he spent nearly 20 years in various senior leadership positions, including President of the Pacemaker Business. Bill has also served as interim President and CEO of MTS Systems (MTSC) a public $SOOM industrial technology company. Bill currently serves on the Boards of MDIC, ILT, Sonex Health and Meso-Flow and previously served on the Boards of MTS Systems, LifeSync Holdings, and ReShape Medical. Bill has also served on various industry association and community leadership boards. He earned a Bachelor of Science Degree in Electrical Engineering from The University of Florida.**
Title of the project	**Patient-Centered Benefit/Risk Assessment : Developing a Useful Methodology for Integrating Patient-Centered Perspectives in Regulatory Decisions**
Presentation Abstract	**Patient Centered Benefit-Risk Project** **Since the 2012 CDRH Benefit-Risk Guidance recommended that sponsors interact with FDA staff regarding the development of patient centered risk-benefit information, there has been increased interest in understanding validated methods and tools for collecting patient preference information and how sponsors should collect and present that information to CDRH. As sponsors seek to include patient preference information as evidence in their regulatory submissions, there is a need to improve the understanding of how to collect and present validated patient centered benefit-risk information.** **A FDA Broad Agency Agreement (BAA) funded the development of a Patient Centered Benefit-Risk (PCBR) Framework developed by the Medical Device Innovation Consortium, a FDA-Industry public-private partnership, one of whose projects is to help investigators and regulators consider the patient perspective on the benefits and risks of medical devices. In order to properly take patient preferences into account, investigators and regulators must have reliable and accurate methods, tools, and approaches to capture and analyze the information to assure the level of evidence required for a regulatory decision. The Framework includes an evaluation of the potential value of patient preference information in regulatory benefit-risk decisions, factors to consider when incorporating patient preferences into regulatory submissions, a catalog of patient preference assessment methods and considerations for incorporating patient preference across the product lifecycle. The Framework is intended to serve as a tool to promote robust patient centered benefit-risk assessment in regulatory submissions.**

Speaker name and title	**John Brownstein, PhD** **Associate Professor, Harvard Medical School** **Co-Founder, Epidemico**
Contractor	**Epidemico, Inc.**
Biography	**Dr. John Brownstein, Ph.D. is Co-Founder at Epidemico, Inc. Additionally, he is an Associate Professor at Harvard Medical School. Dr. Brownstein directs the Computational Epidemiology Group at the Children's Hospital Informatics Program in Boston. He was trained as an epidemiologist at Yale University. Overall, his research agenda aims to have translation impact on the surveillance, control and prevention of disease. He has been at the forefront of the development and application of public health surveillance including HealthMap.org, an internet-based global infectious disease intelligence system. The system is in use by millions each year including the CDC, WHO, DHS, DOD, HHS, and EU, and has been recognized by the National Library of Congress and the Smithsonian. Dr. Brownstein has advised the World Health Organization, Institute of Medicine, the US Department of Health and Human Services, and the White House on real-time public health surveillance. He was awarded the Presidential Early Career Award for Scientists and Engineers, the highest honor bestowed by the United States government to outstanding scientists and engineers. He has authored over a hundred and fifty peer-reviewed articles on epidemiology and public health.**
Title of the project	**Social Media Listening for Adverse Event Surveillance**
Presentation Abstract	**While adverse events are significantly underreported, various social media platforms have given voice to patients who share their experiences with medical products in public forums. MedWatcher Social was developed with support from the FDA to collect, categorize, and analyze such consumer-reported health experiences from social media venues like Facebook, Twitter, and patient forums. It enables regulatory scientists to quickly gain a comprehensive understanding of patient-product interactions in the context of adverse events, as well as consumer sentiments, product switching behavior, off-label use of media I products, and adherence. Our automated vernacular-to-regulatory (MedORA) translations, Natural Language Processing (NLP) and machine learning algorithms are accompanied by manual curation to effectively distill insights from huge amounts of noise and to ensure accurate output reporting.**

Speaker name and title	**Gary A. Hill, Ph.D.** **Vice President** **MANILA Consulting Group, Inc.**
Contractor	**MANILA Consulting Group, Inc.**
Biography	**Over his 40-year career, Dr. Hill has managed multiple concurrent projects with large teams of technical staff involving complex behavioral health and health policy issues. His expertise combines substantive knowledge of research methods, evaluation design, applied statistics, automated data collection, and performance monitoring and reporting systems. For the past 2 decades, Dr. Hill has successfully managed large, complex projects for several Health and Human Services agencies. His recent experience includes directing evidence-based reviews for the National Cancer Institute, the Substance Abuse and Mental Health Services Administration (SAMHSA), and the Administration for Community Living. He currently serves as the project director for a Food and Drug Administration project supporting the agency's initiative related to advancing research and development of regulatory science and innovation. He also recently served as project director for the multiagency, national cross-site evaluation of the Safe Schools/Healthy Students (SS/HS) Initiative and SAMHSA's comparative effectiveness research project investigating the adoption of evidence-based behavioral health programs and practices by primary behavioral healthcare providers.**
Title of the project	**The National Medical Device Curriculum: Supporting Innovation by Enhancing Academic Regulatory Knowledge**
Presentation Abstract	**This presentation will describe the development of a case study-based curriculum that offers instructors the flexibility to tailor lessons to undergraduate and graduate students in diverse fields of study based on local needs and academic requirements and goals. The case study format is similar to that used by the Harvard Business Review. It is a first of a kind initiative to help FDA reach the goal of advancing regulatory science and innovation. The case studies and accompanying instructor guides are being made available to university professors on the FDA Web site who can use hands-on interactive exercises to teach students about regulatory issues, including basic concepts. The curriculum can be used for undergraduate and graduate students enrolled in a certificate or degree programs in engineering, medicine, pharmacology, regulatory science, or public health. Topics include medical device classification, intended use and indications for use, regulatory paths, 510(k), premarket approval, human factors, pre-submission meetings, IDE and clinical trials, quality management system, design controls, combination products, bench testing, animal testing, biocompatibility testing, and adverse events.**

Speaker name and title	**Joseph V. Pergolizzi Jr., MD** **Chief Operating Officer** **NEMA Research Inc.**
Contractor	**NEMA Research Inc.**
Biography	**Dr. Pergolizzi earned a BS in physical chemistry from St. John's University and an MD with highest honors from Ross University School of Medicine. Dr. Pergolizzi completed his residency in anesthesia at Georgetown University School of Medicine and a clinical research fellowship in the Department of Medicine at Johns Hopkins University School of Medicine. He has served as Chief Operating Officer for NEMA Research Inc. since 1997 with global business corporate lead direct responsibilities for turn-key clinical trial management and implementation (Phase I-IV). Prior to joining NEMA, Dr. Pergolizzi was the Director of Business Development and Financial and Affairs for the Johns Hopkins University school of Medicine's Clinical Trials Unit.** **Dr. Pergolizzi is an internationally recognized expert in health economics and outcomes research, pain medicine, anesthesia, internal medicine, clinical research, and drug discovery. He is the author of more than 100 peer reviewed articles, abstracts, platform presentations and book chapters. Dr. Pergolizzi serves as editor-in-chief of The Clinical Researcher, and is an editorial board member or reviewer for many scientific journals including JAMA, Pain Practice, Lancet, and The Scientific World Journal of Anesthesia. He is also an invited feature editor of Pain Medicine. Joseph V. Pergolizzi, Jr., MD, is an adjunct Assistant Professor in the Department of Medicine at Johns Hopkins University School of Medicine, an Adjunct Associate Professor in the Department of Pharmacology at Temple University School of Medicine in Philadelphia, PA, and a senior partner in the Naples Anesthesia and Pain Associates Group of Southwest Florida. Dr. Pergolizzi is the Co-Founder and Chairman of the Board for the Association of Chronic Pain Patients. He is a member of the board of directors and treasurer for the Coalition for Pain Education (COPE), co-founder and Director of Research at the International Pain Research and Treatment Foundation, and a member of the board of directors of the National Institute of Pain, and Always Healthcare. In addition, he serves as Chairman of the Scientific and Research Committee: Poster and Abstract Session for Pain Week, a multidisciplinary international medical conference sponsored by the American Society of Pain Educators, as well as serving as Facilitator and U.S. Board Member for the International Change Pain Initiative, a multidisciplinary Pan-European pain management educational medical consortium composed of globally recognized experts in pain medicine. He is also a committee member of the Food and Drug Administration's Safe Use Initiative and has served on a number of NIH and VA grant review boards.**
Title of the project	**Nurse Pain Educator Pilot Program (NPE): A Method For Improving Communication About Pain Treatment**
Presentation Abstract	**Historically, chronic pain generally went undertreated for a variety of objective and subjective reasons, including: it is difficult to objectively diagnose, it is difficult to manage over a long periods of time, the commonly available medications have potential serious adverse effects, and there are patient-, healthcare-, and societal-concerns over opioid medications. More recently, in an effort to redress the under treatment of pain, the number of prescriptions of opioid analgesics has risen dramatically. However, paralleling the increased legitimate use has been a concomitant increase in opioid abuse, misuse, diversion and overdose related deaths. In an effort to address this problem, one approach has been to redesign opioid formulations and incorporate abuse-deterrent technologies. Though successful, this method has not been able to address the over prescription or over consumption problem with opioids, it has only begun to tackle the abuse and misuse issues. In the FDA Safe Use Initiative's November 2009 report, the FDA cited findings including the number of preventable adverse events due to medication errors, unintentional exposure, drug abuse, misuse, or self-harm may be addressed by educating patients, pharmacists, and clinicians. Keeping this though process in mind, the research goals of this project recognize that opioid abuse, misuse, and diversion may also be reduced through proper prescribing and physician/patient education. Communication between health care professionals (HCP) (including pharmacists) and patients can be greatly improved by: increasing the level of awareness of such things as potential drug-drug interactions; encouraging pharmacists to communicate to patients the importance of proper use and compliance;**

	providing a resource of information to patients and their caregivers; and making available a resource that provides physicians with a comprehensive compilation of tools to aid responsible prescribing of pain medication. Education for all the stakeholders (clinicians, patients, caregivers, administrators, etc.) is the best first step to address the inadequacies that exist in the management of chronic pain today. To provide such education, this program looks to modify existing Nurse Educator models and by doing so will look to provide an opportunity to promote safe and appropriate management strategies. The program will examine the role and impact of a Nurse Pain Educator on the safe and appropriate use of opioid analgesics. More specifically, the program will look to increase the safe and appropriate use of opioid analgesics (e.g., reduced opioid consumption, reduced opioid prescribing) by establishing the Nurse Pain Educator (NPE) as essential figure in the education and management of chronic pain patients who are or will be prescribed opioids.

Speaker name and title	**Garry P. Nolan, Ph.D.** **Rachford and Carlota A. Harris Professor**
Contractor	**Stanford University School of Medicine**
Biography	**Garry P. Nolan, Ph.D. is the Rachford and Carlota A. Harris Professor, Baxter Laboratory for Stem Cell Biology, Department of Microbiology and Immunology, Stanford University; Director, NHLBI Proteomics Center for Systems Biology at Stanford University.** **He trained with Leonard Herzenberg (for his Ph.D.) and Nobelist Dr. David Baltimore (for postdoctoral work for the first cloning/characterization of NF-kB p65/RelA and the development of 293T rapid retroviral production systems). He has published over 180 research papers, is the holder of 17 US patents, and has been honored as one of the top 25 inventors at Stanford University. He has trained more than 30 graduate students and 40 postdoctoral or clinical fellows.** **Dr. Nolan's areas of research include hematopoiesis, cancer and leukemia, autoimmunity and inflammation, and computational approaches for network and systems immunology. His most recent efforts are focused on a single cell analysis advance using a mass spectrometry-flow cytometry hybrid device, the so-call "CyTOF". The approach uses an advanced ion plasma source to determine the levels of tagged reagents bound to cells—enabling a vast increase in the number of parameters that can be measured per cell. Another recent innovation is termed molecular ion beam imaging (MIBI) a system that also uses mass tags that will enable sub-light imaging (5 nm resolution) of tissue sections with 50 or more parameters per image. His laboratory has already begun a large scale mapping of the hematopoietic hierarchy in healthy human bone marrow at an unprecedented level of detail. Dr. Nolan's efforts are to enable a deeper understanding not only of normal immune function, trauma, and other inflammatory events but also detailed substructures of leukemias and solid cancers—which will enable wholly new understandings that will enable better management of disease and clinical outcomes.** **For more information on his lab and their studies visit the Nolan Lab website http://www.stanford.edu/group/nolan/**
Title of the project	**The Immune Atlas**
Presentation Abstract	**Animal models are critical parts of disease modeling and drug development, especially in the context of The Animal Rule. It is critical that we understand the differences between model organisms and humans such that the immunotherapeutics developed in model organisms have the anticipated behavior in humans, and that disease models accurately reflect the immunological events that occur in humans. The low drug approval rate indeed suggests that our animal models are weak links in the drug development process. To help remedy this issue, we are systematically defining the differences and similarities between and within large numbers of healthy humans, mice and three species of non-human primates. Using phospho-flow assays measured by CyTOF mass cytometry, we can interrogate the behavior of all of the major innate immune pathways in all of the major immune cell types simultaneously, including co-variance and cross-talk between these pathways and cells. This is being prepared in the context of an online "Immune Atlas" by which researchers will be able to query datasets prepared under the context of this study and also upload their own datasets for automated comparison. The study prepares the framework for a Human Reference map—the online equivalent of the Human Genome Reference that has propelled genomic studies in the last decade. We expect a similar framework for Immunology will greatly facilitate immune studies in clinical and pharmaceutical medicine as well as basic research.**

Session 5: Chief Scientist Intramural Grant Annual Presentations – 3:10 -4:10 PM

Speaker	**Luisa Gregori, PhD**
Title	**Principal Investigator**

Biography	**Luisa Gregori is a principal investigator in the division of emerging transfusion-transmitted diseases in the Office of Blood since 2008. She has more than 15 years of experience in the field of transmissible spongiform encephalopathies and has focused her research on the risk to blood posed by these diseases. Her area of expertise is on detection and removal of TSE agents from biologicals using animal and biochemical assays. Before joining FDA, Dr. Gregori was assistant professor in the department of Neurology at the University of Maryland in Baltimore where she was also deputy director of the Laboratory of Molecular Neurovirology at the Veterans Affairs Medical Center in Baltimore.**
Subject	**Rapid and Sensitive Detection of Creutzfeldt-Jakob Disease Agents in Tissue and Blood donations**
Presentation Abstract	**Transmissible Spongiform Encephalopathies (TSEs) are rare inevitably fatal neurodegenerative diseases with long asymptomatic incubation periods. Sporadic Creutzfeldt-Jakob disease (sCJD), a human TSE, was transmitted by certain FDA-regulated products such as dura matter, cornea and growth hormones obtained from donors unknowingly infected with sCJD. Currently, tissue donors are not tested for sCJD. Variant CJD (vCJD), a disease most likely caused by dietary exposure to the agent of bovine spongiform encephalopathy, was transmitted by blood transfusion in four cases reported in the UK. No cases of transfusion-transmitted vCJD have occurred in the US; however, a CBER risk assessment has concluded that vCJD risk to blood recipients in the US is small but it is not zero (TSE Advisory Committee, March 2013). FDA has always encouraged the development of a vCJD blood screening test but so far there is no validated vCJD test to identify infected blood donations.** **Our proposal addressed two FDA-regulated products with recognized unmitigated TSE risks: blood and corneas. Aim 1 was to develop a proof-of-principle blood screening test for vCJD. Aim 2 was to adapt commercial rapid prion protein tests to assay cornea donors for sCJD.** **Aim 1** **Our assay targeted abnormal prion protein PrPTSE, the only protein marker of TSE diseases. PrPTSE is present in blood in extremely low concentrations. To overcome this challenge, we had proposed a 2-step strategy. First step was to increase PrPTSE concentration with an in vitro amplification method known as Protein Misfolding Cyclic Amplification (PMCA). The second step was to detect PMCA-PrPTSE product with a very sensitive flow cytometer technology called RAPID-B developed at NCTR. PMCA was capable of amplifying PrPTSE present in a 10-12 dilution of vCJD-infected human brain homogenate to PrPTSE concentrations detectable by Western blot. These results correspond to 6-logs improvement in assay sensitivity compared to our preliminary results. The second step was to incorporate RAPID-B platform to detect PMCA-PrPTSE. This flow cytometer-based technology was optimized at NCTR to detect normal prion protein from diluted normal mouse brain suspensions. However, we were not able to progress on this assay because of unanticipated technical difficulties in the preparation of specific reagents for RAPID-B PrPTSE detection. Fortunately, PMCA alone was capable of direct detection of PrPTSE in infected plasma and we were able to develop a prototype vCJD blood assay.** **Aim 2** **To develop a practical and rapid test to assay the brain of human donors of cornea for the presence of the sCJD agent. We tested two commercial tests. Only Idexx test suitable for a TSE rapid test. in a small panel of human brains, Idexx test reacted only with sCJD brains and discriminated sCJD versus non-sCJD with 100% specificity and 100% sensitivity (5/5 sCJD brains were detected).**

Speaker	**Lauren S. Jackson, Ph.D.**
Title	**Chief, Process Engineering Branch, Division of Processing Science & Technology/Office of Food Safety/CFSAN/FDA**
Biography	**Dr. Lauren Jackson is Chief of the Process Engineering Branch at the Food and Drug Administration (FDA)/Division of Food Processing Science and Technology (DFPST), located in Bedford Park, IL. This division of FDA/CFSAN is part of the research consortium and FDA Center of Excellence, the National Center for Food Safety and Technology (NCFST). Dr. Jackson received her B.S. in Food Science from Cornell University and her M.S. and Ph.D., both in Food Science, from the University of Wisconsin-Madison. Her expertise is in the following areas: the effects of processing on food constituents and contaminants, food allergen control, the stability of biothreat agents, and the analysis and detection of chemical contaminants and constituents in food. Her main area of focus has been on understanding the effects of processing on the formation and destruction of natural toxins in food. She also is one of FDA's subject matter experts on cleaning and other measures for controlling allergens in food manufacturing facilities. Dr. Jackson is actively involved in several committees for the Institute of Food Technologists (IFT) and the American Chemical Society (ACS), and is a member of both societies as well as International Association for Food Protection (IAFP). She is a Scientific Editor for the Journal of Food Science and the Journal of Food Protection.**
Subject	**Optimal Allergen Biomarkers for Effective Assays and Labeling: A Collaborative Project between FDA, IFSH and General Mills**
Presentation Abstract	**Availability of analytical methods to detect and quantify allergens in food is essential for supporting standard setting initiatives, for development of compliance and enforcement activities, and for ensuring the effectiveness of allergen-related sanitation procedures. The main objective of a collaborative project involving several FDA/CFSAN offices, the Institute for Food Safety and Health, and General Mills was to evaluate allergen detection methods (immunochemical and LC-MS/MS) and targets (proteins and peptides) for identification and quantification of milk, egg and peanut allergens in bakery products (muffin and cereal bars) produced in a pilot-scale food production facility from the formulation phase through the packaging phase. Other goals of this project were to 1) evaluate the effectiveness of different cleaning regimens and metrics for such measurements for allergen removal from equipment used in the manufacture of the two bakery products, and 2) study allergen cross-contact into allergen-free bars and muffins from processing lines that were not cleaned after manufacture of allergen-containing products. Analyses of allergen-incurred cereal bar and muffin samples indicate that all of the analytical measurements (immunochemical and LC-MS/MS) underestimated the level of incurred allergen due to thermal processing. Egg protein detected in both bakery products decreased dramatically (>95%) after baking as measured with several ELISA kits. Results obtained for analysis of milk and peanut proteins in samples indicate similar results, although baking did not result in as dramatic a decrease in ELISA detection of milk and peanut proteins as observed for egg. Studies that investigated the effectiveness of cleaning regimens on removing egg, peanut, and milk residue from purposefully contaminated cereal bar and muffin processing lines illustrate the need for validated cleaning protocols for removal of allergenic food residue. A cross-contact study demonstrated that production of cereal bars and muffins on an inadequately cleaned line resulted in transfer of allergenic food residue to subsequently produced products. The information generated in the project is being used by the FDA and the food industry for the identification of optimum markers and development of methods for complete, reliable detection of relevant levels of allergens in complex food matrices such as bakery products and in the food processing environment, to ensure accurate food labeling and effective allergen cleaning/control procedures.**

Speaker	**Qiang Shi, PhD,**
Title	**Visiting Scientist**
Biography	**Dr. Qiang Shi obtained his PhD in pharmacology in Zhejiang University (China) in 2006. His PhD dissertation was on mouse liver protein modifications in drug induced liver injury (DILI). He completed his post-doctoral training in DILI in FDA NCTR from 2007 to 2010, and then became a Visiting Scientist in FDA NCTR in August 2010. Dr. Qiang Shi has a focused research area: mechanisms and biomarkers for DILI. He has nearly 15 years' experience in primary culture of hepatocytes from multiple species. For mechanistic studies, he is mainly working on drug induced mitochondrial damages and metabolism-mediated hepatocyte injury. For biomarker studies, he is using both animal models and human samples to explore novel translational DILI biomarkers, and his work is focused on circulating microRNAs in the urine and blood. He has published 25 peer reviewed manuscripts on DILI.**
Subject	**Urine microRNAs as novel biomarkers for acute liver failure patients**
Presentation Abstract	**Drug induced liver injury (DILI) is the leading cause of acute liver failure (ALF), which carries a high mortality rate. DILI is also a major reason for drug non-approvals, safety warnings or market withdrawals. The FDA endorsed DILI biomarkers lack tissue specificity and novel biomarkers are needed. Though urine microRNAs are intuitively thought and tentatively proven to be potential biomarkers for renal diseases, recent data suggest that they may help diagnose DILI. This study aimed to examine if urine microRNAs in ALF patients are perturbed. Urine samples were obtained for 53 patients and 15 healthy subjects from the Acute Liver Failure Study Group and a commercial vendor, respectively. Customized PCR arrays containing 128 microRNA probes were used to determine the perturbations. Using the criteria of absolute fold-changes > 2 and $p < 0.01$, sixty microRNAs were found to be differentially expressed in healthy and ALF subjects. Principal component analysis of differentially expressed microRNAs showed that the healthy and ALF groups were well separated. The level of 6 microRNAs appeared associated with the death status at 21 days after enrollment, as exemplified by hsa-miR-1260a, whose level was about 4-fold higher in dead patients than alive patients ($p < 0.01$). The levels of 7 microRNAs showed a good correlation to the primary cause of ALF. Specifically, the increase of these microRNAs was similar in ALF patients due to acetaminophen overdose or drug-induced hepatitis, but was significantly smaller in those due to shock/ischemia. For example, the level of hsa-miR-877-5p was increased by more than 1000-fold in drug (including acetaminophen) induced ALF, but the elevation was only about 100-fold in shock/ischemia associated ALF. Interestingly, urine and serum microRNAs seemed not related to each other, as urine microRNA-122 showed no changes despite a sharp increase in the same patients' serum. Urine microRNAs also showed no correlation to the pre-study peak levels of serum alanine transaminase (ALT) or aspartate aminotransferase (AST), though a moderate association between levels of hsa-miR-1228-3p and pre-study peak international normalized ratio (INR) was observed. These data suggest that urine microRNAs may serve as non-invasive complementary biomarkers for human ALF.**

Session 6: CORES Scientific Intramural Grant Presentations – 4:10 -5:00 PM

Speaker	**Peng Zou, Ph.D.,**
Title	**Chemistry reviewer**
Biography	**Dr. Zou is currently a chemistry reviewer at the Immediate Office, Office of Pharmaceutical Quality (OPQ). He received his Ph.D in pharmaceutical sciences from the University of Michigan in 2011 and then performed his postdoc training at the National Cancer Institute. Dr. Zou joined FDA Office of Generic Drugs in 2012 and was responsible for CMC review of nanoparticle products such as iron colloids and liposomes. His current work at OPQ focuses on CMC review of complex ANDA products, PBPK modeling of liposomal products, and internal/external grant management. He has published 40 journal articles, book chapters and three US patents.**
Subject	**Physiologically-based pharmacokinetic (PBPK) modeling of nanomedicine: Building clinically relevant standards for FDA-regulated nanoparticulate drug products**
Presentation Abstract	**Liposomal injections are a main class of nanotechnology drug products regulated by the FDA. There are multiple IND/NDA/ANDA submissions of liposomal products which are under review. To evaluate submissions related to liposomal products, a systematic understanding of the relationships between their physiochemical properties and biodistribution is critical. Physiologically-Based Pharmacokinetic Modeling (PBPK) is an ideal tool to quantitatively describe and predict the biodistribution of liposomal vesicles and drug substances. More specifically, we propose to investigate the quantitative relationships between liposome size/internal contents of ammonium sulfate and liposomal PBPK model parameters. Currently, we have developed mouse and human whole-body PBPK models which can predict the plasma and tissue concentrations and AUC of released and encapsulated doxorubicin with reasonable accuracy after i.v. administration of DOXIL®. In addition, model parameter sensitivity analysis has identified several model parameters which are critical for biodistribution of released and encapsulated doxorubicin. The next step of this study is to establish correlations between liposome size/internal contents of ammonium sulfate and critical model parameters by statistical analysis of animal biodistribution data. The established quantitative correlations will be extrapolated to humans and serve as a potential predictor of biodistribution of liposomal doxorubicin in human.**

Speaker	**Julian E A Leakey, PhD, DABT**
Title	**Research Biologist**
Biography	**Julian Leakey is a research biologist and toxicologist who has worked at NCTR since 1985. He received his PhD in Biochemistry in 1976. His areas of expertise include: drug metabolism, effects of diet and body weight on aging and cancer, toxicology of antiviral drugs, toxicity and efficacy of dietary supplements and immunotoxicology of nanomedicines.**
Subject	**Complement assays for detection of immune-sensitizing activity of nanomaterials**
Presentation Abstract	**The ability to activate the serum complement cascade is a major determinant as to whether a nanoparticle used as a drug or drug-carrier will evoke immunotoxicity. Recently, an in vitro assay for nanoparticle-induced complement activation was developed by G Lanza et al (Pham et al, Nanomed. 10, 651-60, 2014). This Nanotechnology CORES research project is part of an FDA program to beta-test this assay for general use in nanotoxicology research, we have evaluated the assay using a spectrum of coated gold nanoparticles and compared the response of human serum with that of cynomolgus monkey, beagle dog and Sprague-Dawley rat serum. The assay measures residual complement activity in a serum sample by titrating the serum with hemolysin-sensitized sheep erythrocytes and determining the level of hemolysis. The serum samples are pre-exposed to nanoparticles so that the degree of nanoparticle-dependent complement depletion can be determined. The positive control in the assay was coated perflurooctylbromide (PFOB) nanoemulsions (Lanza et al., 2014). The assay provided quantitative and reproducible results with commercially available cryopreserved human and animal serum and with both commercially available and freshly prepared sensitized erythrocytes. Results with PFOB emulsions were correspondent to published data. Species differences were observed in complement activating potential of gold nanoparticles. Human and monkey serum was more sensitive to complement activation than that of dog and rat. In certain cases, particles that activated complement also aggregated in ionic buffers. The data suggests that in vitro species comparisons should be performed prior to designing animal studies to evaluate nanoparticle immunotoxicity. Further work is being conducted to develop a high throughput version of the assay and to develop other ELISA-based assays that can be used to detect complement activation in plasma from experimental animals exposed in vivo.**