2015 FDA Science Forum

Summary Report

U.S. Food and Drug Administration

2015 Science Forum

Date: May 27-28, 2015

Location: FDA White Oak Campus & Webcast

Focus: Emerging technologies in the 8 FDA regulatory science priority areas. These technologies are transforming the development of both technologies and methodologies that FDA uses in its research and regulatory activities and the products it regulates.

Goal: Showcase research at FDA and generate collaboration with industry and academic laboratories to close FDA knowledge gaps and drive innovation in the regulatory science enterprise.

Attendance: About 800 (On-site and remote access by Webcast)

Link to 2015 FDA Science Brochure

Organization of 2015 FDA Science Forum

- **Two concurrent lecture sessions** held each day in the morning and afternoon.
- **All session chairs were FDA scientists**; some presenters were external researchers presenting information of direct relevance to FDA collaborative priorities.
- **Poster sessions were linked to each regulatory science priority** area and held each morning and afternoon in conjunction with that day's lectures (abstracts in forum brochure; see Table of Contents).

- **Videos linked to FDA Science Forum**
    - **Intro blog and video** welcoming potential attendees: Luciana Borio, MD, Acting Chief Scientist, OCS, FDA.
    - **Video available during forum:** Center for Food Safety and Nutrition (CFSAN) researchers Marc Allard and Eric Brown discussing Genome Trakr.
    - **Post-Forum video:** Attendees responded to questions about their impressions of the Forum and the science going on at FDA.
    - **Welcoming remarks at Forum** by FDA Acting Chief Scientist, Luciana Borio, MD (5/27/15).
    - **General remarks at Forum** by FDA Acting Commissioner, Stephen M. Ostroff, MD (5/27/15).
    - **Keynote lecture** by Bert Vogelstein (Johns Hopkins): Cancer Genomes and the Wars against Cancer (5/28/15).

2015 FDA Science Forum: Presentations

Concurrent Session 1 (May 27, 2015)

TOPIC: Ensure FDA Readiness to Evaluate Innovative Emerging Technologies (Session chair: Steven K. Pollack, CDRH, FDA)

FDA is studying powerful new tools and methods that could help it meet the challenge of evaluating products that are emerging through advances in biosynthesis, nanotechnology, materials science, gene therapy, tissue engineering, and information technology.

Breakthroughs in Imprint Lithography and 3D Additive Fabrication (Joseph M. DeSimone, Carbon 3D)

Breakthroughs in the "Makers Movement" do-it-yourself culture use new fabrication tools for rapid prototyping, including an off-shoot of imprint lithography and 3D manufacturing.

Single Cell Methods in Cell Product Characterization (Malcolm Moos, CBER, FDA)

Development of cell-based therapies is complicated by the difficulty of identifying cellular characteristics that predict *in vivo* performance reliably. Many potential therapies contain

more than one cell type; therefore, "population-average" analytical methods are likely to obscure differences between similar cell types and miss the presence of rare cell types. Concepts from developmental, cell, systems biology, and control theory, combined with emerging analytical tools, might enable sufficiently discriminating analysis of cell populations for improving testing and designing improved products and manufacturing processes.

Field Portable Devices – Taking the Laboratory to the Sample (Mark Witkowski, ORA, FDA)

Miniaturize traditional laboratory instrumentation combined with novel technologies has taken sample field analysis to a new level of sophistication and data quality. This presentation gave an overview of field-portable instrumentation, strategies for analyzing samples in the field, and case studies of sample field analysis.

The intersection of Personalized Cardiac Therapies, Cell Based diagnostics and Multi-Variate Physiological Monitoring (David G. Strauss, CDRH, FDA)

Improved diagnostic criteria for safer, precision use of implantable defibrillators and pacemakers; novel electrocardiographic biomarkers of risk for drug-induced arrhythmias; patient-specific induced-pluripotent-stem-cell cardiomyocyte assays to predict clinical trial results; regulatory guidance for next-generation multivariate physiological monitoring devices to overcome faculty predictions of clinical adverse events (e.g., septic shock) that use traditional vital signs and physiological monitors.

Concurrent Session 2 (May 27, 2015)

TOPIC: Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products (Session chair: Lee Zwanziger, OC, FDA)

Using social and behavioral sciences to better inform American consumers and health professionals to help them make sound decisions about using, prescribing, and dispensing products, and thus decrease preventable adverse events linked to FDA-regulated products.

(Move control button at bottom of screen to advance to desired video at times noted after summary of each presentation of this session.)

E-Cigarette Use and Cigarette Smoking Behavior among U.S. Young Adults: A Mixed Methods Study (Blair N. Coleman, CTP, FDA) *(Video starts at 00:00 minutes)*

Research focused on attitudes, beliefs, and perceived social norms of e-cigarettes, as well as openness to conventional cigarette smoking among young adult users of the product: findings provide a basis for further exploration of the association between e-cigarette use and conventional cigarette smoking.

Experimental Study of Patient Information Prototypes (Lt. Oluwamurewa (Murewa) Oguntimein, CDER, FDA) *(Video starts at 00:12 minutes)*

Assessment of single, standardized, patient drug information document prototypes designed to be easy to read and understand; FDA is considering a new regulation to require such a document.

Incorporating Patient Preferences into Regulatory Decision Making (Telba Irony, CDRH, FDA) *(Video starts at 00:22 minutes)*

Obtaining quantitative evidence on how patients weigh risks and benefits of products, and how this evidence could be used in regulatory decision-making.

Recent Findings from Nonhuman Primates on the Long-Term Adverse Behavioral Effects of General Anesthesia When Given During Early Brain Development (Merle G. Paule, NCTR,FDA) *(Video starts at 00:38 minutes)*

Results of studies in rhesus monkeys using the Operant Test Battery (OTB) suggests that a single episode of general anesthesia during a sensitive period of brain development (premature infant, compromised neonate) can cause apparently permanent deficits in primate brain function.

Poster Sessions 1 & 2 (forum brochure, pages 64 & 105)

1. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies

2. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products

Concurrent Session 3 (May 27, 2015)

TOPIC: Facilitate the Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security (Session chair: Rakesh Raghuwanshi, OC, FDA)

The goal of the MCMi Regulatory Science Program is to develop the tools, standards, and approaches to assess medical countermeasure safety, efficacy, quality, and performance, and to help translate cutting-edge science and technology into innovative, safe, and effective medical countermeasures.

Enhancing Preparedness through Novel partnerships for IT innovation: USCIIT-PREP (J. Perren Cobb, Massachusetts General Hospital, Harvard Medical School)

The goal of the United States Critical Illness and Injury Trials Group Program for Emergency Preparedness (USCIITG-PREP) is to facilitate development of medical countermeasures against specific public health threats. FDA's role in this effort is to enhance preparedness by developing and implementing strategies to assess, evaluate, and monitor medical

countermeasure safety, performance, and patient compliance in response to a public health emergency.

Electrophysiological Biomarkers of Brain Injury (Cristin Welle, CDRH, FDA)

The development of diagnostic EEG might enable headsets, such as those currently used in commercial gaming systems, to be used as portable, field-deployable traumatic brain injury (TBI) diagnostic devices. This could allow rapid and accurate screening of injured civilians or service members, greatly advancing the state-of-the-art diagnosis and care of TBI. This study measured EEG characteristics in an animal model of TBI, identifying multiple alterations of EEG characteristics associated with injury.

Pandemic Influenza Preparedness: Development of Novel Technologies for In-Depth Evaluation of Vaccine Efficacy and Long-Term Memory during H7 Clinical Trials (Surender Khurana, CBER, FDA)

Current novel approaches and technologies include studying and improving immune responses to influenza viruses, using adjuvants that increase virus neutralizing titers and heterosubtypic immunity, while affording dose sparing; prime-boost approaches that trigger desired seroconversion; molecular tools (whole genome fragment display libraries and surface plasmon resonance) to study adjuvant induction of epitope spreading from hemagglutinin HA2 to HA1 compared to unadjuvanted or aluminum-adjuvanted, inactivated H5N1 vaccines.

Filovirus Detection and Threat Mitigation (Steven Wood, CDRH, FDA)

Next-generation, chip-based, sequencing (NGS) used to identify filoviruses (FV) and their antigenic drift; model FV vaccine is being used to follow the generation of hunter-killer T-cells. Rapid means of identifying FV and the use of this technology have been developed to unravel the cellular and molecular responses that are altered during the infection. This work will help regulation and evaluation of new FV detection technologies and treatment and can be used in the case of other viruses, such as Middle Eastern Severe Acute Respiratory Syndrome (MERS).

Concurrent Session 4 (May 27, 2015)

TOPIC: Implement a New Prevention-Focused Food Safety System to Protect Public Health
(Session co-chairs: Palmer A. Orlandi, Jr, OFVM, FDA; David G. White, OFVM, FDA)

The Center for Food Safety and Applied Nutrition supports public health efforts to reduce illnesses and deaths in humans and animals by creating new knowledge through research that improves health, nutrition, and safety of regulated products, including human and animal foods and cosmetics. To fill knowledge gaps in these areas of regulatory science, research at the Office of Foods and Veterinary Medicine includes collaborative projects with outside agencies, academic institutions, and industry.

(Move control button at bottom of screen to advance to desired video at times noted after summary of each presentation of this session.)

Food Safety Systems in the Americas: A perspective from the Pan-American Health Organization (PAHO) (Enrique Pérez-Gutiérrez, PAHO) *(Video starts at 00:00 minutes)*

Public health aspects of the food safety system: countries respond to the challenges of food safety tied to the evolution and transformation of food security, agricultural and food industry, international commerce, and the demands of consumers.

GenomeTrakr: A Pathogen Database to Build a Global Genomic Network for Pathogen Traceback and Outbreak Detection (Ruth E. Timme, CFSAN, FDA) *(Video starts at 00:28 minutes)*

GenomeTrakr: pathogen-detection network where state and federal public health agencies share data to build a publicly available and transparent reference data-base with data deposited into a public genomic database (National Center for Biotechnology Information, NCBI). Important investigative role for whole genome sequencing tools within a regulatory environment; provides novel additional insights to epidemiological investigations through comparison to a reference database.

The Nexus of Food Safety, Animal Health, and Antimicrobial Resistance (Patrick McDermott, CVM, FDA) *(Video starts at 00:42 minutes)*

National Antimicrobial Resistance Monitoring System (NARMS): Coordinated by FDA to track resistant bacterial pathogens that arise from the use of antimicrobial agents in food animals and are transmitted to humans via meat consumption; provides more definitive information about emerging bacterial resistances, and the impact of interventions designed to limit or prevent resistance spread; used to evaluate the risks associated with new animal antibiotics to help ensure that antimicrobials remain effective for protecting human and animal health.

The Use of DNA Barcoding to Prevent Species-Specific Foodborne Illness and Detect Seafood Fraud (Jonathan Deeds, CFSAN, FDA) *(Video starts at 01:00 hr)*

Correct species labeling essential FDA's Hazard Analysis Critical Control Point (HACCP) regulation: FDA-initiated Project Fish SCALE (Seafood Compliance and Labeling Enforcements) uses forensic DNA sequencing techniques at its Office of Regulatory Affairs Regional Field Laboratories across the country to verify the identity of seafood products. Enables FDA to respond to claims of mislabeling and fraud, take regulatory action against non-complaint seafood producers and distributors, and enhance rapid response to illness outbreaks linked to seafood.

Non-targeted Screening Methods for Identification of Chemical Hazards of Public Health Concern (Tim Croley, CFSAN, FDA) *(Video starts at 01:16 hr.)*

High-resolution mass spectrometry and data processing algorithms that enable simultaneous targeted and non-targeted analyses of contaminants are promising food monitoring strategies. Major aspects of these approaches include: 1) the impact of chromatography and mass spectrometry conditions; 2) data quality issues; 3) novel data processing algorithms; 4) challenges to minimizing errors in the detection, chemical formula generation, and potential identification of chemical species.

Poster Sessions 3 & 4 (forum brochure pages 112 & 133)

3. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security

4. Implement a New Prevention-Focused Food Safety System to Protect Public Health

Concurrent Session 5 (May 28, 2015)

Topic: Support New Approaches to Improve Product Manufacturing and Quality (Session Co-chairs: Sau (Larry) Lee, CDER, FDA; Carolyn Wilson, CBER, FDA)

FDA collaborates with outside researchers to 1) support development and evaluation of novel and improved manufacturing methods; 2) develop new analytical methods; 3) reduce the risk of microbial contamination of products.

Screening for Counterfeit Pharmaceutical Products Using the CDx Device in Ultraviolet, Visible, and Infrared Modes for Field and Laboratory Use (Nicola Ranieri, ORA, FDA)

The Counterfeit Detection Device (CDx) and methodology developed by FDA rapidly and non-destructively screens for counterfeit pharmaceutical dosage forms and packaging: inexpensive, rugged, portable, hand-held, easy-to-use electronic device enabling 'real-time' rapid screening results in the field and laboratory to examine finished dosage forms and packaging, and tampered, diverted, re-labeled, or re-glued products.

Methods for Detection of Allergens in Food and in the Processing Environment: Approaches and Challenges (Lauren Jackson, CFSAN, FDA)

Analytical tools for detecting allergenic proteins or foods include immunochemical approaches, DNA detection methods, and LC-MS/MS techniques. New approaches are currently under development to improve the reliability of analytical results, and for simultaneous detection of multiple allergens.

Advanced analytics and data integration for comparative biomolecule characterization: A case study of generic enoxaparin (Sau [Larry] Lee, CDER, FDA)

Manufacturers of follow-on (or generic) drug products containing a heterogeneous mixture of molecules or macromolecules must demonstrate similarity (or sameness) of these molecules to those present in the reference products. FDA's review of the Abbreviated New Drug Application pathway for the approval of generic enoxaparin (heparin) demonstrates that, in certain cases, *in vivo* testing in animals and humans could become unnecessary.

Using NMR to Assess Structure and Comparability in Vaccines and Therapeutics
(Daron Freedberg, CBER, FDA)

FDA use of NMR to determine the structural basis of glycan functions by establishing structure-function relationships; descriptions of some of the methods used to characterize protein therapeutics under final container conditions, without resorting to isotopic labels.

Concurrent Session 6 (May 28, 2015)

Topic: Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes (Session chair: Lisa M. LaVange, CDER, FDA)

Bioinformatics, high-throughput screening and powerful new genomic techniques have dramatically improved the efficiency of new drug candidate discovery and development. But targeted therapies using specific genomic technologies to select patients who respond are only in their infancy. The ability to supplement traditional lab testing with clinically meaningful measures that are often based on physiologic, imaging, or genomic endpoints is critical to developing new therapies and ensuring the accuracy and consistency of analytical measurements, while reducing inter-platform and inter-site variability.

(Move control button at bottom of screen to advance to desired video at times noted after summary of each presentation of this session.)

Individualized Therapy as a Practical Aspect of Patient Care (Howard L. McLeod, DeBartolo Family Personalized Medicine Institute, Moffitt Cancer Center) *(Video starts at 00:00)*

Clinically predictive germline variants as objective predictors of patient toxicity to support development of robust risk/benefit models that enable health care providers to decide between apparently equal treatment options for individual patients: Necessary to establish biomarkers that include proteomic or metabolomic strategies and to clarify gene pathways regulating drug activity.

Not in Our Stars but in Ourselves: The Pharmacogenetic Determinants of Immunogenicity of Therapeutic Proteins (Zuben E. Sauna, CBER, FDA) *(Video starts at 00:31)*

Some therapeutic proteins in development are engineered to improve product attributes or enhance process characteristics: Requires generation of neo-epitopes that don't exist naturally and are thus potentially immunogenic. Emerging computational and experimental techniques can potentially be used to assess the immunogenicity risk posed by neo-epitopes to the patient population, as well as to specific patients and ethnic groups. This talk details the cases of a marketed engineered Factor VIII drug product and the discontinuation of the development of a Factor VIIa analog in Phase III clinical trials.

Pharmacogenomics and Biomarker-Based Drug Development (Michael Pacanowski, CDER, FDA) *(Video starts at 00:51)*

Overview of precision drug development, highlighting recent approvals, FDA initiatives, and the evolving regulatory framework.

Statistical Evaluation of "Me-Too" Companion Diagnostic Tests for Selecting Therapies (Gene Pennello, CDRH, FDA) *(Video starts at 01:11)*

Companion diagnostic (CD) tests select patients for a particular therapy: FDA approval of a therapy plus its CD is usually supported by randomized clinical trials (RCTs) of the therapy. After approval of the first CD, a "me-too" or follow-on CD (FCD) may be developed for the same indication: Conceptual talk explores a statistical model for indirectly estimating the clinical usefulness of the FCD by combining FCD-CD agreement data with trial summary data on the clinical usefulness of the CD and feasible post-market study designs.

Poster Sessions 5 & 6 (Forum brochure pages 155 & 187)

5. Support New Approaches to Improve Product Manufacturing and Quality

6. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes

Concurrent Session 7 (May 28, 2015)

Topic: Modernize Toxicology to Enhance Product Safety (Session co-chairs: Donna Mendrick, NCTR, FDA; James Weaver, CDER, FDA)

Need to close critical gaps in preclinical toxicology studies due to serious and sometimes rare adverse events during clinical trials or following product approval: 1) develop better models of human adverse response; 2) identify and evaluate more reliable biomarkers and endpoints for non-clinical and clinical evaluations; 3) use and develop computational methods including *in silico* modeling.

Human Microlivers for Disease Modeling (Sangeeta Bhatia, MIT)

Studies with high-throughput-capable human microlivers that model human drug metabolism, liver disease, and interactions with pathogens have led to the discovery of small molecules that drive proliferation of adult hepatocytes and maturation of stem-cell- derived progeny. This has enabled sourcing of human hepatocytes, and the development of the first high-throughput model systems to study hepatotropic pathogens (e.g. liver stage malaria and hepatitis viral infections).

Discovery and Analytical Validation of System Biology Translation Biomarkers of Toxicity (Richard D. Beger, NCTR, FDA)

New translatable biomarkers must be compared to an established translational biomarker (e.g., ALT) to understand their clinical value. New approaches include e*x vivo* imaging of tissues to discover location of drugs, drug metabolites, and location of metabolomic or proteomic biomarkers related to disease or toxicity. Such data can enhance the sensitivity of other imaging techniques (i.e., MRI/MRS) and be combined with the current non-clinical gold standard – histopathology.

Nonclinical Development of Neurotoxicity Biomarkers Using *in vivo* MRI (Serguei Liachenko, NCTR, FDA)

MRI studies of changes in living rat brain following exposure to one of ten classical neurotoxicants: identified the specific response (change in T2 relaxation) and led to investigation of its specificity and sensitivity against the current gold standard (i.e., histopathology). Results might support development of a sensitive, non-invasive, early biomarker of neurotoxicity that improves drug safety research.

Replacing the Clinical Thorough QT Study with a Panel of In Vitro Assays and Computational Integration (Norman Stockbridge, CDER, FDA)

Remedying the high false-positive rate of pro-arrhythmia assessment that is based today largely on the hERG assay and the "Thorough QT study," described in ICH S7B and E14, respectively. When drugs affect more than one ion channel type, it may be difficult to predict by direct inspection of these data what the net effect would be in the heart. However, these data can be integrated to produce the net effect on the cardiac action potential. This model can then be interrogated to determine how pro-arrhythmic a drug is.

Humanized Hepatic Mice: In Vivo Model to Predict Human-Specific Immunotoxicity, Drug Metabolism and Hepatotoxicity (Kristina E. Howard, CDER, FDA)

Metabolite profiles derived from animal studies can be inconsistent with human responses and the ability to test biologics for safety and efficacy in animal models is limited by differences in biological receptors between species. Potential contribution of human-specific immune responses to the development of immunotoxicity and tissue injury hampers the assessment of product quality. Mouse models with a highly humanized liver and/or an

engrafted human immune system are now being evaluated for their ability to better predict clinical outcomes.

Concurrent Session 8 (May 28, 2015)

Topic: Harness Diverse Data through Information Sciences to Improve Health Outcomes (Session co-chairs: Eric Donaldson, CDER, FDA; Roger G Perkins, NCTR, FDA). Roger Perkins was unable to attend the meeting at the last minute due to a family emergency.

Ability to integrate and analyze all data on product submissions, adverse event reports, de-identified patient data from health care providers, and results from surveys and basic scientific research would enable FDA to extract more new knowledge and insight available from any single source. FDA is constructing the Information Technology (IT) infrastructure to integrate this type of complex data to enable sophisticated data mining for enormous numbers of simultaneous queries of a large set of indexed data sources. This session focused on harnessing Next Generation Sequencing data to improve health outcomes.

Transforming Trillions of Points of Data into Diagnostics, Therapeutics, and New Insights into Disease (Atul Butte, UCSF) *(Video starts at 00:00)*

Translational bioinformatics aims to convert trillions of points of molecular, clinical, and epidemiological data into diagnostics, therapeutics, and new insights into disease. Several of these efforts have been spun out into biotech companies.

Panel Discussion: Next Generation Sequencing Technology at FDA (Moderated by Eric Donaldson, NCTR, FDA) *(Video starts at 00:35)*

Next-generation sequencing (NGS) might enable a single test to identify thousands or even millions of genetic variants in a single individual. The data could then be used to diagnose or predict a person's risk of developing certain diseases. In turn, physicians and patients could determine the treatment that should be used. This could accelerate the development and use of precision ("personalized") medicine. In addition, the reduced sequencing costs associated with NGS are driving industry to adopt this technology over the traditional Sanger sequencing. Analysis of NGS data requires more technical expertise and a greater computational infrastructure.

Atul Butte (UCSF), Carolyn Wilson (CBER, FDA), Hugh A. Rand (CFSAN, FDA), Zivana Tezak (CDRH, FDA), and Weida Tong (NCTR, FDA)

Poster Sessions 7 & 8 (Forum brochure pages 199 & 215)

7. Modernize Toxicology to Enhance Product Safety

8. Harness Diverse Data through Information Sciences to Improve Health Outcomes