The 2023 FDA Science Forum: Advancing Regulatory Science Through Innovation

Date(s): June 13-14, 2023

Location: Virtual

Focus: Novel science and technologies that inform FDA's regulatory decision-making and drive innovation related to FDA-regulated medical products, food, and safety, and tackling critical public health challenges like addiction. Topics covered include use of real-world evidence (RWE), complex innovative trial design (CID), artificial intelligence (AI) and big data, medical countermeasures, and technologies to support pathogen reduction.

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: 5796 Total Participants

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Science Forum Summaries
Session 1: Improving Clinical and Post-Market Evaluation

Session Chair/Moderator: Ruth Barratt, PhD, DVM

Introduction: Ruth Barratt, PhD, DVM, FDA Center for Drug Evaluation and Research
Video segment: 1:34:01 – 1:35:25

Clinical Evidence and Medical Devices: Generating Actionable Evidence from the Real World

Mary Beth Ritchey, PhD
FDA Center for Devices and Radiological Health
Video segment: 1:35:32 – 1:50:57

Per medical device regulations, FDA relies only upon valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective. This presentation will describe considerations for clinical studies generally, to generate valid scientific evidence, then further extend these concepts to assessment of relevance and reliability for clinical studies using RWD. Therapeutic device and digital health examples will be provided, with a focus on the following aspects of studies using RWD: study design and analysis; defining the study population and data elements; completion, accuracy, and timeliness of data; and human subjects protections. Major obstacles (e.g., identifying devices in the absence of structured identifiers in many data sources) and unique opportunities (e.g., integration of patient generated health data) for devices will be highlighted.

CDER/CBER Real-world Evidence Program

John Concato, MD, MS, MPH
Associate Director, Real-world Evidence Analytics, Office of Medical Policy
FDA, Center for Drug Evaluation and Research
Video segment: 1:51:10 – 2:13:31

The evidentiary standard used by FDA to assess the effectiveness of drugs and other medical products was developed based mainly for evidence obtained from clinical trials. In 2016, the 21st Century Cures Act mandated that FDA evaluate the use of real-world evidence (RWE) to help support approval of a new indication for an already approved drug or to help support post-approval study requirements. RWE is clinical evidence regarding the usage and potential benefits and risks of a medical product derived from

analysis of real-world data (RWD). In this context, RWD are data relating to patient health status and/or delivery of health care routinely collected from a variety of sources. This presentation will provide an overview of the Real-world Evidence Program coordinated by FDA's Center for Drug Evaluation and Research. The focus will be on FDA draft guidance published in support of the 21st Century Cures Act and the Prescription Drug User Fee Act VII. Other guidance documents, as well as research projects evaluating the use of real-world evidence, are also discussed.

Real-world Evidence for Vaccine Effectiveness at FDA's Center for Biologics Evaluation and Research

Richard Forshee, PhD
Deputy Director, Office of Biostatistics and Pharmacovigilance
FDA, Center for Biologics Evaluation and Research
Video segment: 2:14:06 – 2:33:49

FDA's Center for Biologics Evaluation and Research has been building our capability to work with real-world evidence (RWE) for many years. Much of the work has focused on studies of vaccine effectiveness. This presentation will review several studies that have applied innovative methods to detect and/or minimize bias in an analysis. These methods include efforts to make cohorts comparable on measured variables, using negative controls, and using linked external datasets to check for balance on unmeasured variables.

Real-world Evidence to Provide Supportive Evidence for Evaluating the Safety and Effectiveness of Therapeutic Products

Sebastian Schneeweiss, MD, ScD
Professor of Medicine and Epidemiology, Harvard Medical School
Division Chief, Pharmacoepidemiology, Department of Medicine, Brigham and Women's Hospital
Video segment: 2:34:09– 3:05:37

Regulatory agencies across the world increasingly consider real-world evidence (RWE) for effectiveness claims in medical product approval and coverage decisions. RWE complements randomized-controlled-trial evidence to understand the effectiveness and safety of medical products in clinical practice by analyzing large longitudinal healthcare data. To support decision-makers, we need (1) full transparency of study implementation, (2) fit-for-purpose data, (3) causal study designs and analyses, and (4) approaches that facilitate the review of RWE studies.

This talk illustrates advances in these areas, with empirical examples and recent regulatory developments.

Panel Discussion
Moderator: Ruth Barratt, PhD, DVM
Panel: Mary Beth Ritchey, PhD; John Concato, MD; Richard Forshee, PhD; Sebastian Schneeweiss, MD, ScD
Video segment: 3:05:48 – 3:35:05

YouTube:
https://www.youtube.com/watch?v=Za0DLkZsos0

Session 2: Product Development Tools and Manufacturing

Session Chair/Moderator: Suzanne Fitzpatrick, PhD

Introduction: Suzanne Fitzpatrick, PhD
Video segment: 3:29 – 4:50

Advancing Drug Discovery with Biofabricated 3D Tissue Models
Marc Ferrer, PhD
Director, 3D Tissue Bioprinting Laboratory
NIH, National Center for Advancing Translational Sciences
Video segment: 4:50 – 35:11

3D tissue models are being developed as predictive efficacy and toxicity assays in early drug discovery and preclinical development. This presentation will discuss work at the National Center for Advancing Translational Sciences' 3D Tissue Bioprinting Laboratory (3DTBL) to create and operationalize a platform of biofabricated 3D tissue models with relevant functional assay readouts to accelerate the discovery and development of therapeutics. The 3DTBL uses human induced pluripotent stem-cells-derived and primary cells, tissue engineering technologies, including bioprinting and tissue chips, to establish a portfolio of biologically validated healthy and disease 3D tissue models of increased physiological complexity as needed to mimic different tissue and organ physiologies and disease pathologies. This presentation will describe examples of the approaches used at the 3DTBL for the versatile and robust production of engineered 3D tissues in multi-well high throughput plate format and their use for disease modeling and compound testing.

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Advancing Translational Models and Tools into the Drug Review Process: Opportunities for MPS

Kevin Ford, PhD, DABT, DSP
Associate Director, Division of Applied Regulatory Science
FDA, Center for Drug Evaluation and Research
Video segment: 35:39 – 50:27

Microphysiological systems (MPS) have gained considerable attention in recent years as promising in vitro tools to recapitulate human physiology by recreating key biological processes and cellular architecture. MPS has proven to be a reliable tool in the drug development process for the investigation of safety assessment; absorption, distribution, metabolism, and excretion; and pharmacokinetics. MPS have become an integral part of the drug development process by many pharmaceutical companies, in part due to (1) the continuous rising costs of developing new drugs, (2) the drive to reduce animal experimentation, and (3) the need for more predictive and high-throughput in vitro models. This presentation will highlight some of the applied MPS research being performed at the Division of Applied Regulatory Science (DARS) in the Center for Drug Evaluation and Research (CDER) at FDA. A discussion of the performance and application of several of the MPS models used in DARS (liver, lung, gut, and heart) was also provided.

Opportunities and Challenges in Using Liver Microphysiological Systems to Study Drug Metabolism and Hepatotoxicity

Qiang Shi, PhD
Visiting Scientist
FDA, National Center for Toxicological Research
Video segment: 50:57 – 1:04:54

Liver microphysiological systems (MPS) are designed to better preserve the functions of in vitro cultured hepatic cells and are emerging as novel tools for the study of drug metabolism and hepatotoxicity. Many types of liver MPS have been published, and some have been recently commercialized. Evidence is accumulating that liver MPS may improve the accuracy in predicting drug hepatotoxicity and metabolism as compared to conventional cell culture, though most findings have not been confirmed by independent studies. Guidelines have been proposed to develop and evaluate liver MPS for possible regulatory use. The challenges, like lack of standardized protocols for toxicity and functional assays and cell qualification, were also discussed.

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Advanced Analytical Methods for Assessing the Efficacy of Regenerative Medicine Cellular Products

Kyung, Sung, PhD
Acting Chief, Cellular and Tissue Therapies Branch, Office of Cellular Therapy and Human Tissue
FDA, Center for Biologics Evaluation and Research
Video segment: 1:05:23 – 1:19:34

Multipotent stromal cells (MSCs) have become popular sources for manufacturing regenerative medicine cellular products, due to their ability to undergo lineage-specific differentiation. MSCs, on the other hand, are heterogeneous and responsive to their surroundings, resulting in distinct subpopulations of cells with potentially different properties required for product potency. Because there are numerous biochemical and biomechanical factors that influence MSC function, developing reliable, high-throughput assays that allow for the efficient exploration of large and complex parameters for evaluating cellular function is critical.

Microphysiological systems offer a viable solution to this unmet need. This presentation will provide an overview of regenerative medicine cellular product regulation as well as easy-to-use, microscale technologies that improve throughput, relevance, and reliability. How such technologies could be used to evaluate the efficacy of regenerative medicine cellular products was also discussed.

Additive Manufacturing: A Case Study in Advanced Manufacturing of Medical Devices

Matthew Di Prima, PhD
Materials Engineer
FDA, Center for Devices and Radiological Health
Video segment: 1:19:53 – 1:33:35

“Additive Manufacturing” (AM) is a blanket term for a suite of manufacturing technologies that use a digital format to build a part layer by layer. While this technology was developed in the early 1980s and commercialized later that decade, it saw little use in medical device production before 2000. From 2010 to 2020, the Center for Devices and Radiological Health (CDRH) stood up a working group focused on AM, had significant stakeholder interactions, published a Guidance, and assumed leadership in AM standards development. As a result, the handful of 510(k) cleared devices utilizing AM technologies in 2010 jumped to over 250 by 2020. To work through this process, the medically relevant AM technologies will be discussed, along with the perceived benefits

of using AM for medical device production. Then, the kinds of 510(k) cleared devices and observed trends in those clearances will be presented from that decade, along with the concurrent standards in development. The presentation concludes with CDRH's activities across that decade to ensure AM device safety and effectiveness.

Enhancing Regulatory Toxicology Decision-making for Tobacco Products: The Role of Computational Toxicology Tools

Luis Valerio Jr., PhD, ATS
Associate Director, Division of Nonclinical Science, Office of Science
FDA, Center for Tobacco Products
Video segment: 1:34:20 – 1:46:36

Computational models are science-based tools showing promise to enhance the quality of regulatory toxicology evaluations of tobacco products. At the Center for Tobacco Products (CTP), these tools have been evaluated to identify respiratory hazards and predict the genetic toxicity and carcinogenic potential of chemicals found in or emitted by tobacco products. Targeted research by CTP's Office of Science (OS), Division of Nonclinical Science (DNCS), has been conducted and published to understand the utility and performance of these tools as applied to chemicals in tobacco products. In these studies, rigorous validation tests and considerations of mode of action have shown the skill of model predictions and correlation with known experimental toxicity outcomes.

This presentation discusses DNCS toxicology research and evaluations by the DNCS Nonclinical Computational Toxicology Program, which suggest the role computational toxicology tools may have in supporting chemical-hazard assessments and risk mitigation of tobacco products. Information about data mining, chemical screening, and good practices for use of prediction models to assess toxicities associated with tobacco products will be highlighted. In conclusion, CTP/OS/DNCS is interested in computational toxicology approaches, when appropriate, to enhance the quality of regulatory toxicology evaluations of chemicals found in or emitted by tobacco products.

YouTube:
https://youtube.com/live/st5vPfzwWtM

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Session 3: Empowering Patients and Consumers

Session Chair/Moderator: Kathryn LaRosa, MPH

Introduction: Kathryn LaRosa, MPH, FDA Center for Tobacco Products
Video segment: 4:33:50 – 4:34:33

Discussion on Increasing the Diversity of Patient and Caregiver Engagement with the Center for Biologics Evaluation and Research on Food Allergy Drug Development

Joey Mattingly, PharmD, MBA, PhD
Associate Professor and Vice Chair of Research, Department of Pharmacotherapy
University of Utah, College of Pharmacy
Video segment: 4:34:40 – 4:50:10

To better understand patient and caregiver engagement with FDA and the diversity of individuals providing input on a therapeutic area involving a drug product regulated by the Center for Biologics Evaluation and Research, the Maryland Center of Excellence in Regulatory Science and Innovation conducted a literature review, environmental scan, in-depth interviews, and a public meeting for patients and caregivers impacted by food allergy. From this work, we identified factors that motivated patients and caregivers to engage with FDA as well as potential challenges or barriers for engagement for different groups of patients. Motivating factors included improving food labeling and food-making processes, educating self and others, having a sense of community, increasing representativeness and having an interest in sharing personal experiences. Barriers for different groups included factors related to cost, travel, time, lack of awareness, and perceived relevance or usefulness. Based on feedback from patients, caregivers, and food allergy advocacy groups, we have identified several opportunities for FDA to improve engagement with this community that may empower different groups to be more involved in FDA's patient engagement activities.

Providing Information Needed to Make Decisions about COVID-19 Vaccines: Qualitative Testing of Educational Materials

Alexandria Smith, MSPH
Social Scientist
FDA, Center for Drug Evaluation and Research
Video segment: 4:50:34 – 5:04:32

After FDA approved COVID-19 vaccines for youths ages 5-11 and 12-15 and those over

age 16, the agency needed to find effective communication strategies for providing information answering pertinent questions about them. To accomplish this, the agency developed a series of educational materials to inform patients' and parents' decision-making about vaccine effectiveness, development, risks and benefits, route of administration, booster eligibility, and corrections to common misperceptions.

Amplifying Equity of Voices: Empowering Patients and Consumers

Julie Hsieh, PhD, MPH
Staff Fellow
FDA, The Office of Minority Health and Health Equity
Video segment: 5:04:57 – 5:17:12

The Office of Minority Health and Health Equity (OMHHE) launched the Enhance Equity Initiative to support research projects and communication efforts to enhance: EQUITY in clinical trials; EQUITABLE data efforts; and EQUITY of voices. In this session, you will learn how OMHHE amplifies Equity of Voices by learning more about OMHHE's diverse stakeholder community, OMHHE-funded research to leverage novel and big data sources to understand diverse patient perspectives, preferences, and unmet needs, and OMMHE's efforts to expand culturally and linguistically tailored health education (e.g., patient, health care provider).

FDA's Closer to Zero Initiative: What Parents Can Do to Help Protect Children from Environmental Contaminants

Kellie Casavale, PhD
Senior Science Advisor for Nutrition
FDA, Center for Food Safety and Applied Nutrition
Video segment: 5:17:32 – 5:35:42

FDA's Closer to Zero initiative takes a whole-of-government approach to reduce the exposure of young children to environmental contaminants, like heavy metals, from foods, and to educate caregivers on the important roles of food variety and nutrition in helping to protect developing children from the potential adverse health effects associated with environmental contaminants. This food safety issue is multifaceted and complex. Food sources of contaminants can also be sources of nutrients essential for child growth and development and include many foods that are part of healthy dietary pattern recommendations of the Dietary Guidelines for Americans. In addition, these contaminants are in the environment where food is grown or raised and removing them

from the environment completely is likely not possible. Attention to this issue, therefore, could have unintended consequences such as parents avoiding foods that are nutritious because they hear the foods are a focus for contaminant reductions. To address these and other challenges, FDA is developing an education strategy, supported by social science research and risk communication theory, to create messages that not only educate and resonate with the public and are grounded in science, but also provide meaningful actions that parents, caregivers, and health professionals can take to support healthy and safe food decisions for families of young children.

Promoting Antimicrobial Stewardship in the Next Generation: Educational Projects Funded by FDA's Veterinary Laboratory Investigation and Response Network

Sarah Peloquin, DVM
Veterinary Medical Officer
FDA, Center for Veterinary Medicine
Video segment: 5:35:56 – 5:48:42

In recent years, antimicrobial resistance (AMR) has become an imminent threat to both humans and animals. Because veterinary use of antimicrobials can have a direct impact on the development of AMR, FDA's Center for Veterinary Medicine (CVM) created a five-year Veterinary Stewardship Action Plan in 2019. One of the primary goals of the initiative is to support antimicrobial stewardship in veterinary settings.

In particular, CVM's Veterinary Laboratory Investigation and Response Network (VetLIRN) contributes to this goal by providing funding to veterinary academic institutions to support antimicrobial stewardship. Vet-LIRN coordinates a network of 46 veterinary diagnostic laboratories across the United States and Canada, and most of these laboratories are located at veterinary schools. By leveraging its existing relationships with veterinary schools, Vet-LIRN is in a unique position to provide funding for the development of educational materials on AMR stewardship.

Since 2020, Vet-LIRN has funded seven grants to five veterinary schools. The seven projects vary in their scope, but all have a common goal of promoting antimicrobial stewardship, including improving access to antimicrobial susceptibility testing, developing stewardship plans, and educating animal owners, veterinary students, and veterinarians. Educating future generations of veterinarians on the importance of using antimicrobials appropriately will play a vital role in the global fight against AMR.

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A Patient-Centered Approach toward the Development of a Patient-reported Outcome Measure
Fraser D. Bocell, PhD, MEd
Social Scientist and Psychometrician
FDA, Center for Devices and Radiological Health
Video segment: 5:49:20 – 6:01:28

Patients are the experts on the symptoms they experience due to their condition. Understanding symptoms of temporomandibular joint disorders (TMDs) can help doctors and patients document, monitor, and manage the disease and help researchers evaluate interventions. Patients with TMDs experience symptoms ranging from mild to severe, primarily in the head and neck region. This study describes findings from formative patient focus groups to capture, categorize, and prioritize symptoms of TMDs toward the development of a patient-reported outcome measure.

Panel Discussion
Moderator: Kathryn LaRosa, MPH
Panel: Joey Mattingly, PharmD, PhD; Alexandria Smith, MSPH; Kellie Casavale, PhD; Sarah Peloquin, DVM; Fraser Bocell, PhD; Julie Hsieh, PhD
Video segment: 6:01:34 – 6:26:45

YouTube:
https://www.youtube.com/watch?v=Za0DLkZsos0

Session 4: Product Development and Manufacturing

Session Chair/Moderator: Hesha Duggirala, PhD, FDA Center for Center for Veterinary Medicine

Introduction: Hesha Duggirala, PhD, FDA Center for Center for Veterinary Medicine
Video segment: 3:03:46 – 3:04:43

Securing Machine Endpoints in a Post-quantum Operating Environment
Jose Arrieta
Chief Executive Officer, Imagineer
Video segment: 3:04:44 – 3:34:22

How to effectively create security around different program logic controllers that exist on machine endpoints is a challenge. The presentation will outline a low-cost effect development, security, and operations approach to creating post-quantum tunnels and security by establishing identities among endpoints at a granular level. The approach will ensure the consistent ability to upgrade inputs into security architecture while delivering at low cost by filling security gaps in the existing architecture.

Reimagining Regulatory Data Submissions through FHIR

Jose Galvez, MD
Deputy Director
Office of Strategic Programs
FDA, Center for Drug Evaluation and Research
Video segment: 3:34:34 – 3:50: 47

The preparation of regulatory submission packages for regulatory agencies is a multi-layered process governed by differing agencies, multiple guidances, complex legal considerations, and not least the coercion of datasets into multiple standards for submission to HAs. While the former is outside of our scope, we will focus on the opportunities for modernization and simplification of the latter.

The current process for the preparation and submission of regulatory data has largely been unchanged for decades. Originally, packages were prepared as correspondences and manuscripts with large amounts of data transcribed onto paper and delivered by the truckload. Regulators were then taxed with the daunting task of combing through the reams of data, validating statistical assertions, and hoping nothing was missed. In today's digital environment, where data is largely produced, stored, and analyzed with the aid of computers, we still ask sponsors to create the same artifacts but have replaced paper with various digital representations. While some data comes nicely packaged in XML or similar formats with known structures and, relatively speaking, is easily transformed from source data system, much data still comes embedded in PDF and DOC formats, which must be "parsed" and interpreted. Modern data representation and transmission standards afford us the opportunity to explore more efficient modes of data transmission. In this talk, we will focus on Fast Healthcare Interoperability Resources as one such technology and its implications to industry and HAs.

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Leveraging Large Datasets for the Development and Evaluation of New AI-enabled Medical Imaging Devices

Frank Samuelson, PhD
Physicist
FDA, Center for Devices and Radiological Health
Video segment: 3:50:48 – 3:59:29

Deep-learning artificial intelligence systems for medical imaging are incredibly complex; some have millions of parameters. These systems function on images, each of which may be many gigabytes in size. To be reliable and generalizable to their intended populations, such systems require training and optimization on very large samples of patient images using very fast computing hardware. Over the last decade several organizations, like the Medical Imaging and Data Resource Center, have amassed large public and private repositories of electronic health records and medical image data. These data have accelerated the development of AI systems that diagnose patients and process medical images. Hundreds of such devices have been submitted to FDA in recent years. Fortunately, these large databases have also facilitated more extensive and rigorous testing of AI systems than was possible just a few years ago. This talk will review and highlight how manufacturers have leveraged these big data resources to develop new artificial-intelligence algorithms and evaluate their safety and effectiveness in submissions to FDA.

Machine Learning and Case Identification in Claims Data

Ravi Goud, MD, MPH
Medical Officer, Office of Vaccines Research and Review
FDA, Center for Biologics Evaluation and Research
Video segment: 4:00:04 – 4:12:26

The accurate detection of outcomes of interest in health-care databases can help harness the potential of big data in health care or public health by enabling the use of available data for surveillance or research purposes. Unfortunately, claims data in health-care databases are meant for administrative purposes, not for research purposes, so the detection of outcomes can be difficult. This is especially true for conditions that can present and be coded in a diverse manner. Machine learning offers a potential solution that permits researchers to take advantage of patterns observed in more dimensions than a human can normally consider.

This presentation covers the experience of using machine learning to help improve

the identification of anaphylaxis, a severe life-threatening allergic reaction, in claims data. Unsupervised and supervised methods were utilized, along with data of varying data quality, as chart-confirmed ground-truth data is frequently rare and arduous to obtain from health-care databases. Based on experience, the speaker proposed a general approach for how machine learning could be used to improve case identification and/or expedite the construction of human expert-driven case identification algorithms.

Using Genomic Data and Machine Learning to Study Antimicrobial Resistance in Foodborne Pathogens

Amy Merrill, MS
Mathematical Statistician
FDA, Center for Veterinary Medicine

Chih-Hao Hsu, PhD
Computer Scientist
FDA, Center for Veterinary Medicine
Video segment: 4:12:37 – 4:23:50

Foodborne enteric bacterial pathogens, which cause disease and illnesses in humans and animals, are now routinely surveilled using whole genome sequencing (WGS). High-resolution genomic data make it possible to link illnesses to specific sources of contamination, and to make predictions about bacterial phenotypes, like virulence and resistance, to antimicrobials. Scientists in the National Antimicrobial Resistance Monitoring System (NARMS) at FDA's Center for Veterinary Medicine use genomic data and artificial intelligence/machine learning to study antimicrobial resistance (AMR) in Salmonella, E. coli, Campylobacter, and Enterococcus, isolated from retail meats, humans, and food producing animals. There is a high correlation between resistance genotypes and phenotypes, allowing for NARMS scientists to use WGS data to predict phenotypic resistance and report on findings as soon as the WGS is completed, without waiting for additional susceptibility testing. NARMS scientists have implemented the Boost Machine Learning Model to improve upon categorical resistance vs. susceptible predictions by predicting antimicrobial Minimum Inhibitory Concentrations from WGS data. The genomic and artificial intelligence/machine-learning work within NARMS allow for rapid, field-based monitoring of emerging resistance genes and mutations, enhanced accuracy in the prediction of AMR, and an understanding of AMR at a deeper level.

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Using Machine Learning to Predict Non-compliance in the Global Food Supply: Improving Risk-informed Resource Allocation and Public Health Protection

Jeffrey Chou, MSPH
Biologist
FDA, Center for Food Safety and Nutrition
Video segment: 4:23:57 – 4:34:40

More than 90% of seafood sold to US consumers is imported from abroad. While the overall supply chain is safe, potential health hazards from seafood include pathogenic bacteria such as Salmonella and toxic compounds from decomposition such as histamines. Thus, machine learning (ML) was chosen as a tool to better predict and increase rates of violative findings in regulatory sampling of imported seafood as part of a pilot study under FDA's New Era of Smarter Food Safety Blueprint.

We trained a ML model using a boosting algorithm (decision tree-based) called LightGBM using 10 years of previous historical sampling data merged with demographic and compliance data of associated source facilities. The model was then used to score active supply chains and products for the probability of violative microbiological and decomposition findings. A 2x2 factorial design was also implemented to understand not only the main effect of the ML predictions, but also the effect of another existing rules-based sampling targeting model running in FDA's systems called PREDICT (Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting).
While the pilot is still ongoing, interim analysis shows that there is a significantly higher violative rate in the samples of products predicted by the model for such hazards vs. those that were not predicted as violative, even when controlling for the effect of PREDICT. This demonstrates the potential and need for expanding the use of ML to other commodities in sampling and other compliance work, like facility inspections, to ultimately maximize public health benefit with limited regulatory resources.

Panel Discussion/ Closing Remarks

Moderator: Hesha J. Duggirala, PhD, MPH
Panel: Steve Condrey, MPS; Joshua Xu, PhD; Yu Mei, PhD
Video segment: 4:34:43 – 5:03:45

YouTube:
https://youtube.com/live/st5vPfzwWtM

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Session 5: Food and Cosmetic Safety

Session Chairs/Moderators: Rajesh Nayak, PhD, FDA, National Center for Toxicological Research

Introduction: Rajesh Nayak, PhD
Video segment: 4:19 – 5:56

ILMERAC: Sharing Scientific Expertise in the Area of Methodologies for Chemicals in Food with National and International Risk Assessment Agencies across the Globe
Djien Liem, PhD
Team Leader
Preparedness, Methodology, and Scientific Support Unit
European Food Safety Authority
Video segment: 5:57 – 35:10

Agencies conducting risk assessments informing regulatory measures in the area of food safety are increasingly working together to keep up with evolution in science. The validation, implementation, and acceptance of potential improvements take time. Cooperation among these agencies will therefore help to address these common future challenges in the area of chemical risk assessment. EFSA therefore proposed, at a conference in November 2017, to bring governmental and intergovernmental organizations together to create the International Liaison Group for Methods of Risk Assessment for Chemicals in Food (ILMERAC).

ILMERAC started its activities in February 2018, with more than 20 agencies, with a regulatory risk assessment mandate to share experience, knowledge, and best practices on ongoing and planned activities aimed at implementing new methods for risk assessment of chemicals in food. Various topics, ranging from the assessment of chemical mixtures to the use of alternative methods to animal testing, were discussed, and participants were given access to all materials considered on a shared repository provided by EFSA. More recently, it was decided to create working groups to have more in-depth discussions on priority topics. A first working group was created to focus on new approach methodologies, and a second working group to address challenges in exposure assessment is currently under consideration.

To date, ILMERAC has brought together more than 80 representatives from 26 organizations to discuss opportunities to integrate new approaches in chemical risk assessment. The achievements of nearly six years of ILMERAC will be summarized.

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Progress and Needs for New Alternative Methods in CFSAN's Regulatory Mission

Steven M. Musser, PhD
Deputy Center Director for Scientific Operations
FDA, Center for Food Safety and Applied Nutrition
Video segment: 36:00 – 53:04

CFSAN recognizes that global partnerships are important in advancing the development and acceptance of New Alternative Methods (NAMs). The International Liaison Group on Methods for Risk Assessment of Chemicals in Food (ILMERAC) was created through a partnership with FDA and the European Food Safety Authority, with the goal of facilitating and coordinating research and regulatory efforts on NAMs through an international framework that could provide the best path to harmonized outcomes. Since its creation three years ago, food regulators from other countries have joined including Japan, China, Korea, Singapore, and Canada. ILMERAC's first challenge was to identify cover key data gaps with NAMs, thus minimizing the need for animal studies. Mixtures were identified as a global problem. ILMERAC's second challenge is to provide guidance for using non-guideline studies (i.e., peer-reviewed publications), including harmonized reporting, and to explore the "context of use qualification" approach. ILMERAC's third challenge is to address the evolution of the risk assessment paradigm, facilitating the integration of mechanistic information rather than apical endpoints at the end of a study. Once case studies using these NAMS are available, the global partners will solicit input from relevant stakeholders.

Studies to Assess the Virulence of Enteric Foodborne Pathogens

Steven Foley, PhD
Division Director, Microbiology
FDA, National Center for Toxicological Research
Video segment: 54:05 – 1:08:50

Salmonella enterica and Escherichia coli are significant causes of foodborne disease worldwide, and many efforts have been made to minimize their impact on human health. The rapid adoption of whole genome sequencing (WGS) for the characterization of these pathogens has provided a wealth valuable data to better understand factors that increase their pathogenicity (virulence). To more fully utilize WGS data, NCTR scientists have developed virulence factor databases and analytical tools to identify putative virulence genes within sequenced strains. These efforts created a user-friendly web-based interface that allows users to upload WGS files, either singly or as a batch, to determine

the genes present. Results from these bioinformatic analyses can then be used to try and correlate the WGS findings to detected virulence phenotypes using in vitro, clinical and/or epidemiological approaches.

This presentation provides results of studies that have utilized WGS analyses, coupled with in-vitro, culture-based assessment of intestinal epithelial cell invasion and persistence, comparisons of human clinical strains to those from food animals, and strains with different disease phenotypes to assess virulence. In many cases, there is a good connection between the sets of genes predicted through the WGS analyses with the observed virulence phenotypes; however, in other cases, it is not as clear, highlighting the need for continued research and novel approaches to understand virulence.

An Update on NCTR and OCAC's Collaborative Efforts to Support Cosmetics Safety Evaluation

Luísa Camacho, PhD
Deputy Director, Division of Biochemical Toxicology
FDA, National Center for Toxicological Research
Video segment: 1:09:29 – 1:21:55

Cosmetics (products designed to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering appearance, as defined in the Food, Drug, and Cosmetic Act of 1938) are regulated in the United States by FDA. To help support this regulatory mission, FDA's National Center for Toxicological Research (NCTR) maintains a diverse research portfolio related to cosmetics safety evaluation, developed in close collaboration with FDA's Office of Cosmetics and Colors (OCAC). Ongoing studies will be presented to showcase NCTR's multidisciplinary approach to address regulatory data gaps identified by OCAC and to evaluate novel tools, including human-relevant, non-animal in vitro test systems, which may ultimately be adopted to inform the safety profile of cosmetic ingredients. This FDA cross-center research collaboration addressing New Approach Methods is ever more relevant with the recent enactment of the Modernization of Cosmetics Regulation Act of 2022, which enhances FDA's regulatory oversight of cosmetics and emphasizes that Congress has a sense that animal testing should not be used for safety testing on cosmetic products, with the exception of appropriate allowances.

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The US National Antimicrobial Resistance Monitoring System: Helping Ensure the Efficacy of Antibiotics

Patrick McDermott, PhD
Senior Science Advisor for Antimicrobial Resistance
FDA, Center for Veterinary Medicine
Video segment: 1:22:30 – 1:40:17

The National Antimicrobial Resistance Monitoring System (NARMS) is an interagency program of the US government that tracks antibiotic resistance in foodborne bacteria from foods, animals, and human clinical cases using harmonized methods. NARMS is moving toward a One Health model of resistance monitoring, which incorporates data on environmental surface waters. Research studies comparing whole genome sequencing (WGS) and classical susceptibility testing data for NARMS target bacteria demonstrated a very high concordance between clinical resistance and the presence of known antimicrobial resistance genes. Therefore, WGS has become the primary data set for AMR monitoring in NARMS, with genomes being uploaded into the public domain on a continuous basis in near real time. Data science tools developed at CVM are helping to track resistance at the genetic level and to foster rapid communication and response. Research into metagenomic methods is also being used to catalogue the resistome from various relevant biological samples, including environmental waters. The use of both genomic and metagenomic approaches is providing new insights into the ecology of antibiotic resistance and helping to establish best practices for One Health antibiotic resistance monitoring in the age of genomics.

Panel Discussion

Moderator: Rajesh Nayak, PhD, MS
Panel: Djien Liem, PhD; Steven M. Musser, PhD; Steven Foley, PhD; Luísa Camacho, PhD; Patrick McDermott, PhD
Video segment: 1:40:18 – 2:06:11

YouTube:
https://www.youtube.com/watch?v=filMu1ugSFo

Session 6: Medical Countermeasures, Infectious Disease and Pathogen Reduction Technologies

Session Chairs: Jenna Osborn, PhD (CDRH); Monica (Burts) Young, PhD (CBER); and Mugimane Manjanatha, PhD (NCTR)

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Introduction: Mugimane Manjanatha, PhD, FDA, National Center for Toxicological Research
Video segment: 6:29 – 9:07

Investing in the Future of Health Security

Sandeep Patel, PhD
Director, Division of Research, Innovation, and Ventures
HHS, Biomedical Research and Development Authority
Video segment: 9:20 – 29:45

The Biomedical Advanced Research and Development Authority (BARDA) is an operating division under the Administration for Strategic Preparedness and Response of the Office of the Secretary in the Department of Health and Human Services (HHS). BARDA's role is to develop medical countermeasures needed to respond to public health emergencies (PHE) from a variety of threats. BARDA's Division of Research, Innovation, and Ventures (DRIVe) works at different stages of development, taking risks on unusual or undervalued technologies and approaches that lay critical groundwork for PHE response, with impact beyond a particular product. In addition to R&D programs, DRIVe also creates ecosystems to encourage and support development through novel models of partnerships, including accelerator networks and nonprofit venture capital investments.

FDA ARGOS: Where Trusted Sequence Data Meets Quality by Design Approach

Vahan Simonyan, PhD, DSc
Chief Scientist, Embleema
Professor of Bioinformatics and Biostatistics, George Washington University
Video segment: 30:50 – 49:40

Effective diagnosis and understanding of infectious diseases through next generation sequencing (NGS) requires an extensive and high-quality reference sequence database. To address this critical need, FDA's Medical Countermeasures Initiative has spearheaded project ARGOS. The mission of FDA ARGOS is to create a high-quality, regulatory-grade annotated reference sequence database of biothreat organisms, emerging pathogens, and clinically significant bacterial, viral, fungal, and parasitic genomes; and to provide high provenance, reproducible analytical tools for improving FDA's ability for regulatory evaluation of NGS diagnostic devices using ARGOS data. The project delivers to the regulatory and scientific community various benefits:

1. A high-quality database for reference-grade pathogen sequences.

2. Quality control (QC) metrics and comprehensive annotations for all sequences.
3. Standardized dictionaries for NGS-based sequence QC metrics.
4. Harmonized tools for sequence QC, annotation, and deposition.

Assessing the Role of T-Cell Responses in SARS-CoV-2 Protection

Marian Major, PhD
Principal Investigator and Laboratory Chief, Laboratory of Hepatitis Viruses, Office of Vaccines Research and Review
FDA, Center for Biologics Evaluation and Research
Video segment: 50:18 – 1:05:19

Correlates of vaccine-induced protection against SARS-CoV-2, and especially the role of T cells, remain incompletely defined. Using mouse models, we are studying vaccination with self-amplifying RNAs (saRNA) encoding the SARS-CoV-2 spike protein or adenovirus vectors expressing the nucleocapsid protein (Ad-N) to further evaluate immunity to COVID-19. Vaccination of K18 transgenic mice with the saRNA expressing spike induced both antibody and T-cell responses that provided protection following viral challenge, in terms of less weight loss, less viral burden, and improved survival. However, these protective outcomes were accompanied by increased inflammation in lungs due to T-cell and B-cell infiltration. Both the protective effects and the inflammatory increases depended on the availability of T cells at the time of challenge. Conversely, vaccination of mice with Ad-N vectors did not result in increased lung inflammation following challenge despite reduced weight loss and lower lung RNA titers. The quality and magnitude of T-cell responses induced during vaccination could be pivotal in the development of vaccine-enhanced respiratory illness for COVID-19 vaccines.

Development of Regulatory Science Tools to Accelerate Development of Medical Devices in Public Health Emergencies

Jenna Osborn, PhD
Scientific Project Manager, Office of Science and Engineering Laboratories
FDA, Center for Device and Radiological Health
Video segment: 1:08:46 – 1:24:10

The Office of Science and Engineering Laboratories (OSEL) is composed of scientists and engineers who have a broad diversity of expertise from microbiology to artificial intelligence and machine learning. In OSEL, researchers work to develop Regulatory

Science Tools (RSTs), which are peer-reviewed resources for companies to use where standards and MDDTs do not yet exist. These tools expand the scope of innovative science-based approaches to help improve the development and assessment of emerging medical technologies. Within OSEL, the Emergency Preparedness Program conducts regulatory science research to help ensure patient access to innovative emergency preparedness devices that are safe and effective. This presentation will include an overview of RSTs and the ongoing work within OSEL's Emergency Preparedness Program.

Development of a Platform Approach to Model Neurotropic Viral Infections and Characterize the Therapeutics That Target Them

Daniela Verthelyi, MD, PhD
Chief, Laboratory of Innate Immunity, Office of Biotechnology Products
FDA, Center for Drug Evaluation and Research
Video segment: 1:25:05 – 1:47:42

Combating emerging new viruses or virus variants would benefit from testing systems that keep up with the evolution of the viruses, while providing consistent measurements of therapeutic activity. Thus, we are developing a platform mouse model that can be used by sponsors to assess the impact of drug products on viral clearance, disease progression, and long-term sequelae of emerging viral infections in vivo using common readouts. Recently, we adapted the platform to develop mouse models for the evolving SARS-CoV-2 and its major variants of concern, and we confirmed the selective therapeutic activity of different monoclonal antibodies. Recognizing that the need to conduct in vivo studies under BSL3 conditions can delay product development and testing, we then generated a BSL2-compatible in vivo system for enveloped viruses using replication competent, GFP tagged, recombinant vesicular stomatitis virus (VSV), where the glycoprotein of the VSV was replaced by the SARS-CoV-2 spike protein (rVSV-SARS2-S). These models induce symptomatic productive infections that are characterized by neuronal infection and encephalitis, with increased expression of interferon-stimulated genes in the brain and are uniformly lethal. While the spike protein in different variants are determinants of infectability and virulence, the platform approach may allow for the use the same biomarkers of therapeutic efficacy, reducing the turnaround time for validating each model.

Evaluation of Testicular Organoids as a Model for Zika Virus Infection

Dayton Petibone, PhD

Research Biologist, Division of Genetic and Molecular Toxicology
FDA, National Center for Toxicological Research
Video segment: 1:48:17 – 2:05:20

Zika virus (ZIKV) can infect testicular cells, replicate, and be sexually transmitted through seminal fluid and sperm, even in the prolonged absence of viremia. ZIKV infected women who may be or become pregnant might experience pregnancy problems, including fetal loss or congenital Zika syndrome. However, no anti-ZIKV therapies or vaccines are currently approved for use. Here, we describe development and evaluation of non-human primate (NHP) M. mulatta in vitro testicular organoids (NHp-TOs) for use as a model of ZIKV infection. We demonstrated NHP-TO formation and functionality and its susceptibility to ZIKV productive infection for up to 21 days in culture. The system was also suitable to measure testosterone, inhibin B levels, and cytokine secretion, thus demonstrating NHp-TOs to be an appropriate model for studying kinetics of ZIKV infection and pathogenesis in vitro. Such a system will be useful for the evaluation of potential therapies, including anti-viral drugs and antibodies, for treatment of ZIKV infection in the male reproductive system.

Panel Discussion
Moderators: Jenna Osborn, PhD; Mugimane Manjanatha, PhD
Panel: Sandeep Patel, PhD; Vahan Simonyan, PhD, DSc; Marian Major, PhD; Daniela Verthelyi, MD, PhD; Dayton Petibone, PhD
Video segment: 2:05:32 – 2:09:44

YouTube:
https://youtube.com/live/C8DrLhfr8TE

Session 7: Advancing Products Based on Novel Technologies

Session Chairs/Moderators: Julie Schneider, PhD (OCE); and Mugimane Manjanatha, PhD (NCTR)

Introduction: Mugimane Manjanatha, PhD
Video segment: 3:07:47 – 3:09:09

Update on Personalized Cancer Vaccines
Catherine J. Wu, MD
Professor of Medicine, Harvard Medical School

Chief, Division of Stem Cell Transplantation and Cellular Therapies, Department of Medical Oncology, Dana-Farber Cancer Institute
Video segment: 3:09:35 – 3:39:09

Multiple lines of evidence have convincingly demonstrated tumor neoantigens as an important class of immunogenic tumor antigens, and have motivated the development of personalized cancer neoantigen targeting approaches. Neoantigens arise from amino acid changes encoded by somatic mutations in the tumor cell and have the potential to bind to and be presented by personal human leukocyte antigens molecules. As a field, we have now successfully moved beyond the first wave proof-of-concept studies that have demonstrated the safety, feasibility and high immunogenicity of these personalized vaccines. An imperative now is to address the challenges of discovering and optimizing the selection of antigens to target the delivery approach, and extending this promising approach to a broader array of cancer settings.

Use of NGS Technologies in B-cell Receptor-based Immunome Profiling and MRD Biomarker Discovery

Wenming Xiao, PhD
Lead Bioinformatics Scientist, Office of Oncologic Diseases
FDA, Center of Drug Evaluation and Research
Video segment: 3:40:05 – 3:52:37

With the rapid development and adaptation of next-generation sequencing (NGS) technologies, we have the unprecedented opportunity to interrogate many fundamental and transformative questions surrounding the adaptive immune system and human disease. The convergence of high-throughput sequencing technologies, novel analysis methods, and advancements in immunotherapy and drug development has set the stage for standardizing the quantitative study of human immune cell receptor repertoire composition and diversity. The overarching study objectives of this research proposal are to elucidate current limitations, address fundamental technical challenges, provide reference samples and data sets, and establish best practices for reconstructing B-cell receptor repertoires from NGS data. Specifically, with sequencing of contrived samples using short and long-read sequencing technologies, we will critically evaluate and compare sequencing platform, BCR gene mapping/alignment, clonotype classification, diversity, and convergence method and tool to provide best-practice standards and a state-of-the-art analysis framework for B-cell profiling and MRD discovery.

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Host-microbiome Crosstalk: Disruption of Gastrointestinal Barrier as Toxicity Assessment Tool

Sangeeta Khare, PhD
Research Microbiologist
FDA, National Center for Toxicological Research
Video segment: 3:53:26 – 4:12:19

The human body is exposed to several xenobiotics on a daily basis, including food additives, pesticides, herbicides, drugs, and several other environmental and food contaminants. Exposures to xenobiotics may impact the gastrointestinal barrier and lead to disruptions in the abundance and function of microbiome, antimicrobial resistance, gut mucosa-associated responses, or longer-term disease states. The aim of the research group is to define criteria and build a decision tree for the toxicological assessment at the gastrointestinal tract. The presentation will discuss ongoing approaches, challenges, and opportunities to establish science-based minimum standards for conducting hazard analyses of such products using animal and nonanimal models. The outcome of this research will lead to knowledge-based evaluation of xenobiotics using innovative emerging technologies to modernize toxicology.

Regulatory Perspectives on Advancing Regenerative Medicine Products and Emerging Technologies

Carolyn Yong, PhD
Associate Director, Policy and Chief, Policy and Special Projects
Staff, Office of Therapeutic Products
FDA, Center for Biologics Evaluation and Research
Video segment: 4:12:55 – 4:24:40

Regenerative medicine is an interdisciplinary field, which aims to restore, replace, or regenerate diseased or damaged cells, tissues, or organs using biological or cell-based technologies. This continuously growing area of biomedical research encompasses cell biology, tissue engineering, drug delivery, and advanced manufacturing, among others. The field of regenerative medicine has made remarkable progress from bench to bedside, bringing reduction in disease burden to patients with limited to no therapeutic options. FDA has oversight of a diverse array of Regenerative Medicine Therapies (RMTs) intended to treat or cure diseases or medical conditions and many of which incorporate or utilize novel technologies. The scientific novelty of RMTs present unique challenges for meeting regulatory requirements. Further, advanced technologies implemented in the development of RMTs can have a significant impact on product development, the manufacturing process, and control strategies, and may also have

regulatory implications. FDA plays a critical role in translating innovations into novel, safe, and effective medical products that improve public health.

Dermal Drug Delivery via Dissolvable Microneedles: Formulation Variables Affecting CQAs

Nahid S. Kamal, PhD, MS
Pharmacologist, Office of Testing and Research, Office of Pharmaceutical Quality
FDA, Center for Drug Evaluation and Research
Video segment: 4:25:17 – 4:43:37

Dissolving microneedle (DMN) arrays are a micron-sized needle shape dermal drug delivery system that bypasses the stratum corneum following insertion into the skin to deliver drug. Developing DMNs that have desirable critical quality attributes (CQAs), especially optimal mechanical properties to ensure skin insertion and optimal drug release, remains a challenge. To this end, it is important to identify formulation and/or process variables that may impact these CQAs for successful development of DMN arrays and subsequent progression from the bench to the bedside. Our presentation will highlight critical formulation variables (polymer to drug ratio) which may affect the topographical characteristics, drug distribution in the microneedles, mechanical properties (fracture force and skin-piercing ability of the microneedles) and the drug release characteristics of DMN arrays. Our presentation elucidates the microneedle technology, scientific criticality of its formulation and manufacturability, and the quality aspects that may impact the product performance. The audience learns how artificial intelligence (AI) segmentation may be employed to assess the topographical characteristics and drug distribution in a DMN array. Additionally, this presentation provides insight into a novel discriminatory drug release testing method for DMNs. Overall, the presentation oversees the challenges and successes associated with various characterization approaches for assessing the quality and performance of DMNs.

Assessment of Trabecular Bone Stiffness Using Radiomics and Deep-learning Features

Qian Cao, PhD
Visiting Scientist, Division of Imaging, Diagnostics, & Software Reliability
Office of Science and Engineering Laboratories
FDA, Center for Devices and Radiological Health
Video segment: 4:44:27 – 4:57:10

Evaluation of bone fracture risk is important for the diagnosis and treatment of

osteoporosis. Bone stiffness is one major factor in determining bone strength and fracture risk. With recent improvements in the spatial resolution of computed tomography (CT) imaging systems, it is possible to visualize bone microstructure and extract texture features. These texture features can be used to construct artificial intelligence/machine learning (AI/ML) models to predict stiffness.

In this work, we developed models utilizing deep learning features, radiomics features, and gradient structure tensors to estimate trabecular bone stiffness in high-resolution CT. We applied these texture-based models to a dataset of trabecular bone region-of-interests (ROIs) extracted from lumbar vertebrae micro-CT images. For each ROI, we used its simulated appearance in high-resolution CT to predict finite element analysis-derived stiffness. We show that texture features can be used to improve the assessment of stiffness compared to using bone mineral density alone. These features may be useful as part of a novel imaging-based biomarkers for osteoporosis therapy studies, potentially streamlining clinical trial designs.

Panel Discussion
Moderators: Mugimane Manjanatha, PhD
Panel: Catherine J. Wu, MD; Wenming Xiao, PhD; Sangeeta Khare, PhD; Carolyn Yong, PhD; Nahid Kamal, PhD; Qian Cao, PhD
Video segment: 4:57:31 – 5:04:52

YouTube:
https://www.youtube.com/watch?v=filMu1ugSFo

Session 8: Substance Use, Misuse, and Addiction

Session Chair/Moderator: Arit Harvanko, PhD, FDA Center for Tobacco Products

Introduction: Marta Sokolowska, PhD
Video segment: 3:09:39 – 3:15:19

Abuse Liability Testing with Humans: A Review of Standard Methods and Recent Innovations Using Cigarettes Varying in Nicotine Content as an Exemplar

Stephen T. Higgins, PhD
Virginia H. Donaldson Professor of Translational Science, Departments of Psychiatry & Psychological Science, University of Vermont
Director, Vermont Center on Behavior and Health

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Video segment: 3:15:57 – 3:54:24

This presentation provides an overview of methods used in human abuse liability testing using standard and more recent innovations in test methods. Controlled, double-blind, experimental studies conducted to assess whether reducing the nicotine content of cigarettes alters their abuse liability will be reviewed. Testing was conducted with adult volunteers who were current daily cigarette smokers, selected from populations known to be highly vulnerable to chronic smoking, nicotine dependence, and associated adverse health impacts of smoking. Methods to be reviewed include standard subjective-effects questionnaires and drug self-administration procedures as well as more recent and innovative methods such as the hypothetical cigarette purchase task (CPT), wherein experienced users estimate how much product they would consume under varying prices. Results from studies using these standard and more recent methods in the same experiments will be reviewed. Additionally, studies using the more conventional acute testing arrangement, as well as extended exposure testing, will be reviewed.

Blunt and Non-blunt Cannabis Use Associated with Cigarette, E-cigarette, and Cigar Initiation: Findings from the Population Assessment of Tobacco and Health Study

Heather L. Kimmel, PhD
Health Scientist Administrator/Project Officer and Director of the Population Assessment of Tobacco and Health Study, Division of Epidemiology, Services, and Prevention Research, Epidemiology Research Branch
NIH, National Institute on Drug Abuse
Video segment: 3:55:23 – 4:05:36

Smoking cannabis using a tobacco-derived cigar shell or wrap, called “blunt smoking,” exposes its users to non-trivial amounts of nicotine. The extent to which smoking blunts impact the risk of initiating other tobacco products is not well understood. We investigated if past-year blunt smoking is related to the risk of initiating cigarettes, e-cigarettes, and cigars.

Field-deployable Analytical Toolkit for Rapid Analysis of FDA-regulated Products at International Ports of Entry

LT Martin M. Kimani, PhD
Senior Regulatory Research Officer
FDA, Office of Regulatory Affairs

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Video segment: 4:06:09 – 4:17:19

In 2021, 128.9 billion units of mail were processed by the United States Postal Service, and many of these items were parcels containing potentially dangerous unknown, unapproved, and misrepresented drug products regulated by FDA. To increase the number of products inspected and help protect consumers, FDA's Forensic Chemistry Center launched a satellite laboratory program outside of the Chicago International Mail Facility (IMF). Two analysts permanently staff this satellite laboratory and analyze samples for the presence of active pharmaceutical ingredients (APIs) onsite, using an analytical toolkit that was extensively evaluated for ruggedness, ease of use, and speed during a pilot study. This toolkit consists of a handheld Raman spectrometer, a portable FT-IR spectrometer, and a portable ambient ionization source, coupled to a mass spectrometer, which has detected over 250 unique APIs in drug products seized during the pilot study and production program.

This program was originally implemented to target opioids, particularly fentanyl and fentanyl analogs, but it has evolved over time to include any type of FDA-regulated products, with an emphasis on complete unknown samples without any type of labeling, which can be challenging even in a traditional brick and mortar lab with an arsenal of well-established analytical techniques. Over the course of 16 months (6/21/2021-10/1/2022), over 1,500 samples were analyzed, and violative samples were referred to compliance for possible regulatory action, which helped prevent over 350,000 dangerous lot units from reaching the US supply chain. The APIs detected in these samples were either unapproved, controlled substances, and/or fell under the scope of section 801(u) of the Food, Drug and Cosmetic Act, which are drug products that have been deemed by FDA to pose a significant public health concern. Several samples for which the toolkit yielded inconclusive results were sent to a traditional FDA lab for additional/confirmatory analysis.

Here, we delve into the relative merits and limitations of each device, describe the ongoing optimization of the workflow, examine the lessons learned, and discuss plans for future permanent satellite laboratories located at other IMFs.

Leveraging Systems Modeling to Inform Policies on Opioids

Sara Eggers, PhD
Director, Decision Support and Analysis Staff, Office of Program and Strategic Analysis
Office of Strategic Programs
FDA, Center for Drug Evaluation and Research

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Video segment: 4:17:43 – 4:27:48

Making meaningful gains in the opioid crisis requires interconnected interventions — policies, technologies, services, and communications — all working together. However, assessing the potential public health impact of any one intervention in isolation is extremely challenging in light of incomplete information, complex underlying social phenomena, and the ever-changing opioids landscape. In response to 2017 recommendations from the National Academies of Sciences, Engineering and Medicine, FDA is undertaking efforts to incorporate a systems approach into considerations about the public health impacts of the opioid crisis.

As part of these efforts, FDA has developed, in collaboration with a research team from Harvard/Massachusetts General Health, a national-level system dynamics simulation model of the opioid crisis called SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects). SOURCE is intended to help FDA and other stakeholders identify high-impact interventions concerning opioid misuse prevention, opioid harm reduction, and treatment for opioid use disorder; to assess intended and potential unanticipated consequences of potential policies; and to identify needs for further research. SOURCE has been designed for use within a broader policy analysis service that leverages qualitative and quantitative systems modeling approaches as part of the toolkit of resources informing FDA's policy assessments. The effort has already contributed data-driven insights on underlying trends of the opioid crisis and the potential future effects of broad policy strategies that have informed policy assessments and have helped to advance the use of systems thinking more broadly.

Public Health Harms from Prescription Stimulant Diversion and Nonmedical Use

Rose Radin, PhD, MPH, BS
Team Lead, Office of Surveillance and Epidemiology, Division of Epidemiology
FDA, Center for Drug Evaluation and Research
Video segment: 4:28:42 – 4:43:11

This talk presents the following:

1. Trends in the medical use and nonmedical use of prescription stimulants indicated for attention-deficit/hyperactivity disorder.
2. Motivations, perceptions, and behaviors related to prescription stimulant nonmedical use, with a focus on young adults.
3. Harms from nonmedical use of prescription stimulants and illicit stimulants.

4. Concerns about increasing illicit fentanyl and methamphetamine in falsified stimulant products that illicit sellers offer online and may be difficult to distinguish from legitimate prescription products.

Barriers to Prescribing Buprenorphine as a Medication for Opioid Use Disorder: Health-care Providers' Practices, Perspective and Experiences

Matthew Walker, DrPH
Social Scientist, Office of Communications, Research and Risk Communications
FDA, Center for Drug Evaluation and Research
Video segment: 4:43:36 – 4:54:29

Medications such as buprenorphine and methadone can help decrease cravings and relieve withdrawal symptoms for patients with opioid use disorder (OUD), a chronic health condition that can be life-threatening, but which is also treatable. To address the significant and growing U.S. opioid addiction and overdose crisis, the federal government in early 2020 eased restrictions on prescribing buprenorphine as a medication to treat OUD. Despite removing the extensive training requirement and need for a special Drug Enforcement Agency waiver to prescribe it for up to 30 patients, the number of clinicians prescribing the medication did not increase.

As part of a qualitative research project led by the Office of Communications within FDA's Center for Drug Evaluation and Research, 16 focus groups (N=143) were conducted among primary care physicians (n=65); physician specialists (n=43); psychiatrists (n=7); physician assistants (n=19), and nurse practitioners (n=9) in late 2021 and early 2022. Qualitative analysis of this feedback was conducted to identify potential barriers to prescribing buprenorphine as MOUD.

Three main barrier-related themes emerged from the data: (1) lack of self-confidence in participants' ability to prescribe buprenorphine, (2) the inconvenience surrounding the practical implications of prescribing the drug and treating patients with OUD, and (3) perceived negative outcomes resulting from prescribing buprenorphine, like the need for intensive follow-up, potential side effects, and a general lack of knowledge about the drug.

These findings provide an increased understanding of barriers to buprenorphine prescribing practices among US health-care providers that can be used by FDA and others to design educational information and interventions and help inform regulatory actions that can support and advance new and better treatments for people with OUD.

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Neonatal Opioid Withdrawal Syndrome: A Scientific and Regulatory Update

An N. Massaro, MD
Supervisory Medical Officer
FDA, Office of the Commissioner
Video segment: 4:54:49 – 5:08:23

Neonatal opioid withdrawal syndrome, or NOWS (also commonly known as "neonatal abstinence syndrome," or NAS) can occur following in utero transfer of opioid medications or non-prescription opioids to the fetus. Incidence of NOWS is increasing alongside the broader opioid use disorder (OUD) epidemic in the US. Addressing OUD and NOWS are priorities of the Department of Health and Human Services, with ongoing programs including the Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome Studies and the HEALthy Brain and Child Development (HBCD) Study specified as part of the National Institutes of Health's Helping to End Addiction Longterm (HEAL®) Initiative.

Recent and ongoing nonclinical and clinical research have helped to increase our understanding of the pathogenesis, clinical course, and long-term neurodevelopmental impact of NOWS. At the same time, knowledge gaps remain and contribute to ongoing challenges with medical product development for treatment of NOWS. Challenges include the reliability of standard methods to assess NOWS severity, clinical variability in approaches to pharmacologic and non-pharmacologic interventions, and selection of clinically relevant endpoints to measure effectiveness of pharmacologic agents and medical devices intended to treat NOWS. This talk will provide an overview of recent and ongoing studies and discuss challenges in developing new therapies aimed at improving outcomes in neonates with NOWS.

YouTube:
https://youtube.com/live/C8DrLhfr8TE