The 2021 FDA Science Forum: Science as the Foundation for Protecting and Promoting Public Health

Dates: May 26-May 27, 2021

Location: Virtual

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

Day 1- May 26, 2021 Virtual Webcast
Total 10,940 views
Total Peak Concurrent Viewers and 1637

Day 2- May 27, 2021 Virtual Webcast

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Total 3,376 views
Total Peak Concurrent Viewers 600

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

Session Chair/Moderator: Julie Schneider, PhD, OCE/FDA

Introduction: Julie Schneider, OCE/FDA; Steven Berman, CDER/FDA; John Scott, CBER/FDA; Dong Wong, NCTR/FDA
Video segment: 0:00 -- 3:26

Between Marketing Approval and Appropriate Use of Medical Products--Time to Transform the System

Robert M. Califf, MD, MACC Head of Clinical Policy and Strategy, Verily and Google Health
Adjunct Professor, Duke University and Stanford University
Video segment: 3:27 -- 30:14

Estimating the balance of benefits and harms associated with medical products requires empirical evidence supplemented by models to interpolate where direct evidence is not available. The transition into the modern digital world creates opportunities to improve direct, empirical evidence and modeling and algorithms. It is now possible to improve every aspect of randomized trials: identifying research participants, collecting high-quality simple data at scale, capturing complex biological data, and assessing outcomes and follow up. Diverse populations can be enrolled without requirement for expensive and cumbersome travel to specialized research clinics and many trial procedures can be accomplished using digital collection of data. Additionally, improvement in EHR/claims data and streaming of real-time data enables new procedures for identifying participants and applying algorithms to implement trial procedures. Finally, the vast increase in capacity for data and automated curation leads to the ability to model for expected outcomes, facilitating improved trial design and better estimates of synthetic control groups or "digital twins" in single arm studies. Use of real-world data and real-world evidence across the spectrum of trial designs is moving quickly, but the fundamental importance of randomization to control for unmeasured confounders and time bias should not be underestimated.

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Applications for Surveillance: Interrogating Whole-Genome Sequence and CAERS Data

James Pettengill, PhD, CFSAN/FDA
Video segment: 30:50 -- 47:28

The FDA Center for Food Safety and Applied Nutrition (CFSAN) helps safeguard more than $1.5 trillion worth of food, cosmetics, and dietary supplements. CFSAN's work includes modernizing methods to find, track, and eliminate harmful germs and other hazards; investigating causes of foodborne illness outbreaks; and targeting unsafe products. The world is awash in data and it is an ongoing challenge to extract and harness the information content of public databases. Data Science provides a toolkit for harnessing information content and communicates findings to stakeholders and decision-makers. This talk gives examples of ways to interrogate data to detect signals of interest to further CFSAN's public health goals. Two dashboards written with R Shiny have been developed to help interrogate and surveil data sources containing potential signals of interest to public health related to foods, cosmetics, and dietary supplements. The AEFinder uses the open EBGM (Empirical Bayes Geometric Mean) method for determining disproportionality scores for adverse event data mining; the Pathogen Detection Surveillance application is a lightweight tool for querying a large whole-genome sequence database of foodborne pathogens. These applications highlight the use of statistical methodologies to mine data sources for a signal and illustrate the power of relatively simple applications to facilitate surveillance efforts in the interest of protecting public health.

Regulatory Science/Research Needs Related to Digital Health

Bakul Patel, MSEE, MBA, CDRH/ FDA
Video segment: 47:53 -- 1:03:45

The FDA Center for Devices and Radiological Health (CDRH) protects and promotes public health by ensuring timely patient access to high-quality, safe and effective medical technologies. The Digital Health Center of Excellence's (DHCoE) goal is to empower stakeholders to advance health care by fostering responsible and high-quality digital health innovation. Recent activities within the DHCoE include holding public listening sessions and publishing an artificial intelligence/machine learning action plan that intends to further a practical regulatory framework for modifications to artificial intelligence/machine learning-based software as a medical device. Meeting regulatory science/research needs related to digital health is important for advancing the goals of the DHCoE to foster responsible innovation of digital technologies for protecting and promoting public health. Mr. Patel discusses how digital technology may increase our understanding of certain determinants of health, addresses cybersecurity and interoperability, and lays out a landscape of digital health solutions.

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Regulatory Applications and Research of Model-Informed Drug Development (MIDD)

Yaning Wang, PhD, CDER/ FDA
Video segment: 1:04:14 – 1:21:49

The pharmaceutical industry has applied a model-informed drug development (MIDD) strategy to new drug development. The number of submissions, including various applications of MIDD method, has increased exponentially in the last two decades. Decisions related to dose optimization (including for sub-populations), patient selection, and drug approval have been supported by MIDD methods ranging from empirical data-driven models and semi-mechanistic models to fully mechanistic pharmacology models. MIDD was incorporated into PDUFA VI as one of the key initiatives. This talk provides an overview of regulatory applications of and research on MIDD from the clinical pharmacology perspective and describes how MIDD may play a critical role in future analysis to support personalized medicine.

Including Non-Concurrent Control Data in Bayesian Adaptive Platform Trials When Temporal Changes Exist

Min (Annie) Lin, PhD, Statistical Science Director, Astra Zeneca
Video segment: 1:22:32 – 1:40:30

Temporal changes exist in clinical trials. As time evolves, shifts in patients' characteristics, trial conduct, and other features of a clinical trial may occur. Temporal effect can be a serious obstacle for conducting clinical trials with complex innovative designs, such as the adaptive platform trials (APTs) that are gaining popularity in recent medical product development and that may be especially useful for studying diseases or conditions with unmet medical needs. The overarching design of APTs is capable of simultaneously studying multiple treatments for a disease indication using a shared control arm. With APTs, non-concurrent control data will be available for the pairwise comparisons between the shared control arm and any newly added treatment arms. How to utilize the non-concurrent data while adjusting the clinical heterogeneities caused by any temporal changes has been statistically challenging. Dr. Lin introduces a Bayesian robust prior for mitigating temporal effects while incorporating non-concurrent control data in the APT framework. Simulation studies to evaluate the performance of the proposed method in various scenarios are presented.

Panel Discussion

Moderators: Dr. Steven Berman
Panel: Dr. Robert Califf; Dr. Annie Lin; Mr. Bakul Patel; Dr. James Petengill; Dr. Yaning Wang
Video segment: 1:40:54 – 2:00:19
Session 1: Improving Clinical and Post-Market Evaluation

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Science Forum Summaries
Session 2: Tools to Effectively Use Big Data

Session Chair/Moderator: Donna Mendrick, PhD, NCTR/FDA

Introduction: Donna Mendrick, NCTR/FDA
Video segment: 0:00 – 0:16

Democratizing Screening & Diagnostics with AI
Lilly Peng, M.D., PhD, Physician-Scientist, Product Manager, Google Health
Video segment: 0:16 – 22:14

Deep learning has shown significant promise in healthcare. In particular, the technique has been able to yield highly accurate models and make novel predictions, often with short turnaround, in a variety of medical imaging applications such as detecting cancer, skin, and eye disease. Despite this promise, progress has been slow and much of the hard work of translating exciting research into tangible patient benefit still lies ahead. This talk covers lessons learned and work in progress, including concepts around model training, translation of research into products, and real-world implementation. Dr. Peng dispels three common myths about building and translating artificial intelligence (AI) models for healthcare.

Developing a Deep Learning MedDRA encoder (MedDRA-DeepCoder) for Patient Narratives
Qais Hatim, PhD, Data Scientist, CDER/FDA
Video segment: 22:17 – 37:40

Patient narratives reported in clinical study reports provide evidence of adverse events and help scientific reviewers during pharmacovigilance activities. Manual review of these narratives can be a daunting task for safety reviewers because it is time-consuming and resource intensive. How can we improve the efficiency of identifying safety signals from patient narratives? Can deep-learning technology help to overcome the review challenges in an automated way? Investigators applied four deep-learning methodologies and one machine-

learning methodology to narratives from the FDA Adverse Event Reporting System (FAERS) to determine which methods could best assess a safety signal in the narrative data. The results indicate that deep learning and machine learning can supplement existing response cycles to adverse events identified in clinical study reports, both for medical coding and to characterize issues associated with syndromes.

CBER BEST: Leveraging AI to Build an Automated Adverse Event Reporting System

Hussein Ezzeldin, PhD, Senior Staff Fellow, Office of Biostatistics and Epidemiology, CBER/FDA
Video segment: 37:45 – 54:27

Current adverse-event reporting systems for biological products have multiple challenges related to the burden of manual reporting, no direct data connection, under-reporting for certain products, and inconsistences in the quality of reports. CBER launched the Biologics Effectiveness and Safety Innovative Methods (BEST IM) initiative to address these challenges, advance and improve post-marketing adverse event reporting, and ensure safety and effectiveness of biological products while reducing the reporting burden. The initiative leverages automation and innovative technologies and semi-automated medical chart review. BEST IM is leading efforts to develop a portable and scalable infrastructure (BEST Prototype), and fit-for-purpose methods to automatically detect, validate, and based on electronic health records, report adverse events that may be associated with biological products. The Prototype uses a robust data quality assurance plan with 200+ data quality checks to ensure that the data meet regulatory-grade data requirements. It uses artificial intelligence, machine learning, and natural language processing to develop predictive models to detect exposures and outcomes of interest in electronic health records. The BEST chart review tool extracts the flagged data and presents the suspect case for clinical review. BEST IM developed and validated 6 complex phenotypes, with an average positive predictive value greater than 90 percent. CBER continues to enhance the capabilities of the Prototype.

Development of a Data/Text Analytics Tool to Enhance Quality and Efficiency of Bioequivalence Assessment

Meng Hu, PhD, Scientific Lead, CDER/FDA
Video segment: 54:37 – 1:09:15
Enhancing quality and efficiency of bioequivalence (BE) assessment will facilitate generic drug approval, particularly considering the large number of abbreviated new drug application (ANDA) submissions received and the Office of Generic Drugs' commitment to meet regulatory assessment timelines under the Generic Drug User Fee Amendments (GDUFA) II program. To

address the need for more efficient, consistent, and high-quality assessments, the Office of Generic Drugs led efforts to develop a data/text analytics tool, Bioequivalence Assessment Mate (BEAM). The BEAM tool automates labor-intensive work during the BE assessment by streamlining categorization of submission documents, data preparation, routine BE statistical analyses, and table-filling using information supplied by applicants. With several mouse clicks, the tool can generate a data and text-populated BE assessment report that assessors can use to finalize the review. The developed functions are derived from R and SAS data analytics, text mining, machine learning, and artificial intelligence technologies. Functions are integrated within the R-shiny framework to provide a user-friendly graphic interface for BE assessors. The tool has been used by BE assessors for ANDA reviews during the pilot, making the ANDA BE assessment process more efficient and consistent. This work demonstrates promising potential to use advanced data/text analytics tools to enhance regulatory assessment and improve business intelligence at the FDA.

Trade-off Predictivity and Explainability for Machine Learning-Powered Predictive Toxicology: An In-Depth Investigation with Tox21 Data Sets

Leihong Wu, PhD, Visiting Scientist, NCTR/FDA
Video segment: 1:09:34 – 1:24:09

Selecting a model in predictive toxicology often involves a trade-off between prediction performance and explainability: should we sacrifice the model performance to gain explainability, or vice versa? Dr. Wu presents a comprehensive study to assess algorithm and feature influences on model performance in chemical toxicity research. The investigation included more than 5000 models for a Tox21 bioassay dataset of 65 assays and approximately 7600 compounds. Investigators employed 7 molecular representations and 12 modeling approaches varying in complexity and explainability to systematically examine the impact of various factors on model performance and explainability. Results demonstrated that endpoints dictated a model's performance, regardless of the chosen modeling approach. Overall, more complex models performed marginally better than simpler models. Because a simpler model with acceptable performance is often also easy to interpret for the Tox21 dataset, it was clearly the preferred choice due to its better explainability. To identify models and balance predictivity and explainability, it is important to conduct a systematic study with a broad range of model complexity and feature explainability.

Use of Machine Learning to Improve Food Safety Quantitative Microbial Risk Assessment

Hao Pang, PhD, Biologist, Office of Analytics and Outreach, CFSAN/FDA
Video segment: 1:24:24 – 1:39:46

Quantitative Microbial Risk Assessment (QMRA) can inform food safety decisions by evaluating the magnitude of the change in risk from application of different mitigations or control measures. One key component in QMRA is to develop predictive microbiological models to estimate the survival and growth or die-off of microorganisms under different environmental or food storage conditions during the farm-to-fork continuum. Machine learning can be effectively used to improve the accuracy of predictive microbiological models and QMRA estimates. Dr. Pang uses a recent study to demonstrate the application of machine learning in QMRA research. By developing a machine learning model using a large-scale dataset from a multi-year longitudinal field experiment, the investigators estimated the survival of *E. coli* O157:H7 in soil amended with untreated biological soil amendments of animal origin. The model captured various *E. coli* O157:H7 survival patterns and accurately predicted the concentration of *E. coli* O157:H7 over time under dynamic environmental conditions. The model can be used for similar pathogens such as salmonella. Machine learning is a powerful modeling approach that can be combined with mechanistic models to embrace the strength of both methods to improve predictive microbiology, QMRA, and food safety research.

Role of Artificial Intelligence in Medical Imaging

Berkman Sahiner, PhD, Biomedical Research Scientist, CDRH/FDA
Video segment: 1:39:55 – 1:58:56

There is great potential for artificial intelligence/machine learning (AI/ML) in medical imaging to improve healthcare. As a reflection of this potential, a large percentage of the AI/ML-enabled devices that have been authorized by the FDA have focused on the analysis of medical images. AI/ML was originally used in this area for computer-aided detection and diagnosis, which aim to help clinicians improve image interpretation. Recent years have seen a rapid expansion of the use of AI/ML in medical imaging, with newer applications that include computer-aided triage, clinical decision support, image reconstruction/denoising, image acquisition guidance, quantitative imaging, and now potentially autonomous devices. Rapid advances in the medical imaging AI/ML area are accompanied by challenges in how the FDA can further foster the development of these devices while ensuring they are safe and effective. This talk provides examples of recently authorized medical imaging AI/ML devices and explores newer challenges and regulatory questions brought about by the use of data-driven methods for AI/ML-enabled device training and testing. Dr. Sahiner discusses research conducted at CDRH to address these challenges, including those in image triage, image reconstruction, quantitative imaging, training/test data sets, the definition/generation of the ground truth, and new studies in computer-aided detection and diagnosis.

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Science Forum Summaries
Session 3: Empowering Patients and Consumers

Session Chairs/Moderators: Christine Lee, PharmD, PhD; Andrea Furia Helms, MPH
Video segment: 0:00 – 0:54

Introduction: Andrea Furia Helms, OC/FDA
Video segment: 0:54 –11:00

Listening Sessions to Uncover Patient Questions: The COVID-19 Vaccine Confidence Project
Susan Winckler, JD, Chief Executive Officer, Reagan Udall Foundation (RUF)
Video segment: 11:16 – 26:11

The number of vaccine-hesitant Americans continues to be a concern, particularly in the context of COVID-19. Investigators conducted a landscape analysis to identify key themes in media surrounding COVID-19 vaccine hesitancy. They then conducted listening sessions with vaccine-hesitant individuals to understand concerns about COVID-19 vaccines and inform FDA's Center for Biologics Evaluation and Research about messages and messengers they might employ to respond effectively to those concerns. Listening session participants were from traditionally underrepresented populations and essential workers. Through themes that emerged from these sessions, 10 messages were developed, tested, and refined and categories of the most effective messengers were identified. The investigators developed recommendations for FDA and other public health experts to provide information and dispel myths and misconceptions. The top messengers identified were local doctors, nurses, and pharmacists as well as other health experts. The recommendations provided through this study are an effective way to understand vaccine hesitancy, help start a conversation, and provide consumers with information about COVID-19 vaccines.

Understanding Perceptions and Attitudes About COVID-19 Testing in Under-Represented Populations

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Jessica Weinberg, MPP, CDRH/FDA
Video segment: 26:24 – 36:30

Many racial and ethnic minorities are disproportionately affected by COVID-19, with higher proportions of COVID-19 cases, hospitalizations, and deaths. To better reach these populations and mitigate the spread of COVID-19, it is critical to develop accurate and meaningful communications about COVID-19 testing and encourage participation in national data collection efforts. The FDA Center for Devices and Radiological Health (CDRH) partnered with the University of Maryland Center of Excellence in Regulatory Science and Innovation to conduct a qualitative study to better understand perceptions in underrepresented populations about COVID-19 testing and data sharing, identify barriers to getting tested, and inform message development about COVID-19 testing. Investigators conducted 16 focus groups with participants from these populations: African Americans, native Spanish speakers, older adults, individuals with lower literacy, individuals with chronic conditions, and asymptomatic individuals with household members who tested positive for COVID-19. Findings focus on participants' knowledge and experiences with COVID-19; perceived benefits and concerns about testing; enabling and hindering factors to getting tested; motivations for getting tested or not; and understanding COVID-19 test results. Participants also shared suggestions for content and modes of communicating with their communities. These results may help CDRH, FDA, and other public health agencies tailor approaches to achieve the most effective messaging.

COVID-19 and Tobacco Use: The Latest from the Population Assessment of Tobacco and Health Study

Yu-Ching Cheng, PhD, CTP/FDA
Video segment: 36:50 – 47:14

The Population Assessment of Tobacco and Health (PATH) Study collects information on tobacco-use patterns, health, and other factors. This nationally representative, longitudinal cohort study of approximately 46,000 youth and adults in the United States began in 2013, with data collection occurring annually. In late 2020, the PATH Study added a special collection among a nationally representative sample of adults 20 years and older to examine trends in use of cigarettes and electronic nicotine delivery systems (ENDS) and associations between COVID-19 and tobacco use. This presentation 1) provides prevalence estimates of tobacco products for adults over multiple waves of data (2013 to 2020); 2) describes initiation, cessation, and transition across selected tobacco products; 3) describes product characteristics such as device types and flavor use; and 4) reports on tobacco use during the COVID-19 pandemic.

Impact of COVID-19 on FDA Orphan Products Grants

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Christine Mueller, DO, OC/FDA
Video segment: 47:27 – 58:26

FDA's Office of Orphan Products Development (OOPD) in the Center for Drug Evaluation and Research (CDER) funds clinical trials and natural history grants to defray the costs of developing drugs, biologics, medical devices, and medical foods for rare diseases or conditions (21 U.S. Code § 360ee). The ~$17 million Orphan Products Grants Program is an incentive program that has been supporting clinical trial research since 1983 and has facilitated the marketing approval of over 70 products for rare diseases. The program has also committed funding to natural history studies since 2016 to help address the lack of natural history data for rare disease product development. These grants support both academic- and industry-sponsored research, domestic or foreign, public or private, and for-profit or nonprofit entities. The disease must be rare as defined in the U.S. Orphan Drug Act (21 U.S. Code § 360ee(b)(2)). At any one time, there are typically 60 to 85 ongoing grant-funded projects. OOPD began hearing concerns about study progress due to the COVID-19 pandemic in March 2020. OOPD began tracking these issues to determine the effects of the pandemic on the program and supported studies. Seventy-nine percent of studies were impacted by the COVID-19 pandemic. Effects included study suspension, study/grant completion delays, addition of virtual capabilities, site and/or protocol changes, budget and travel implications, and study endpoints not being assessed. OOPD/FDA offered guidance on conducting clinical trials during the public health emergency; arranged opportunities for grantees to discuss with each other how they were handling issues; and issued administrative supplements to help with unexpected increases in costs. OOPD is continuing to monitor the impact of COVID-19 as the landscape changes and adjust grants programs to increase impact, promote innovation, and learn from the past.

COVID-19 Pandemic: Adjustments to Ongoing Clinical Trials

Wilson Bryan, MD, CBER/FDA
Video segment: 58:39 – 1:09:28

FDA's Center for Biologics Evaluation and Research (CBER), Office of Tissues and Advanced Therapies (OTAT) regulates the development of a diverse portfolio of products, including cellular and gene therapies, for the treatment of a wide variety of clinical disorders. The number of of investigational new drug applications (INDs) submitted to OTAT increased dramatically during the COVID-19 pandemic, with substantial interest in developing cellular products and cellular-derived products for treating COVID-19. Several factors have also forced or enabled adjustments to ongoing clinical trials. These factors include the risks associated with in-person study visits during the pandemic, the expense of conducting trials in the setting of the pandemic, and the emergence of telemedicine and wearable devices. As a result of these factors, clinical trial sponsors have proposed and/or implemented changes in both conduct and

analysis of trials. Adjustments in ongoing trial conduct have had an impact on study recruitment and enrollment, informed consent, monitoring, and endpoints. Proposed adjustments to the analysis of ongoing trials have included reconsiderations of sample size, study duration, interim analyses, and missing data. Based on experience with ongoing trials during the pandemic, lessons learned focus on the usefulness of telemedicine and the importance of communication between regulators and drug developers.

FDALabel – An FDA Product Labeling Tool Enabling Patients and Consumers Safety in Combating COVID-19

Hong Fang, PhD, NCTR/FDA
Video segment: 1:10:20 – 1:21:40

FDA drug product labeling provides essential scientific information for safe and effective use of FDA-regulated products. Labeling includes indications, warnings and precautions, dosage and administration, and patient use instructions. FDALabel is a user-friendly tool that provides quick and reliable access to current product information, including COVID-19-related products, for patients, researchers, regulators, and healthcare professionals. The FDALabel database tool, hosted through Amazon Cloud, manages ~135,000 FDA Structured Product Labeling (i.e., electronic digital labeling) documents with intuitive and powerful functions for querying and information retrieval and is integrated with other databases. Currently, of FDALabel's 4,205 COVID-19-related labeling documents, 4,191 are hand sanitizers and disinfectant wipes registered as OTC drugs, and 14 are prescription drugs and vaccines. Using vaccines as an example, the investigators analyzed labeling data for the Pfizer-BioNTech and Moderna COVID-19 Vaccines (authorized under FDA's EUA), which includes their safety data (e.g., clinical trial data, storage information, and dose administration.

Patient Focus Groups to Enhance Communications Addressing Biosimilar Drug Products

Brian Lappin, MA, CDER/FDA
Video segment: 1:21:50 – 1:32:10

Chronic diseases, such as cancer, are the leading cause of death and disability in the United States. It is critical to develop evidence-based educational materials that can raise awareness, understanding, and appropriate use of medical treatments to improve the quality of life for individual patients and society more broadly. This can be challenging when novel treatments become available. To communicate more effectively about new drugs called biosimilars, which are expected to increase access to treatments that target some chronic diseases, FDA conducted 10 focus groups (N=78) with patients that could be treated with these products to collect evidence related to their knowledge, attitudes, experiences, and desires when communicating with healthcare professionals, and about information needs. Patients reported

little to no knowledge about biosimilars. The information desired most included their effectiveness compared to a current medication, whether side effects are different or fewer than their current medication, and reasons for switching to a biosimilar aside from potential cost savings. Patients provided feedback on a draft infographic concerning language; message meaning, comprehension and relevance; format, and images. Understanding patients' baseline knowledge, attitudes, and information needs is key to identifying effective ways to educate them about novel treatments that can improve individual and public health. FDA is soliciting and using input from patients to develop and enhance materials, particularly by providing basic information in plain language needed to answer their questions and allay fears and uncertainties. This kind of effective communication can enhance patient decision-making and increase access to lifesaving treatments.

Addressing Demographic Subgroup Underrepresentation in Oncology

Lola Fashoyin-Aje, MD, MPH, OCE/FDA
Video segment: 1:32:20 – 1:45:45

This presentation provides an overview of the Oncology Center of Excellence's (OCE's) programs designed to increase participation of underrepresented groups in oncology clinical trials, the importance of diverse representation in clinical trials, and general access barriers to clinical trial participation. Traditionally underrepresented groups include older adults; pediatric patients; racial, ethnic, sex, or gender minority groups; populations located in rural areas; and in some cases, urban populations. Dr. Fashoyin-Aje describes OCE's Project Community, Project Equity, Project Silver, and Project Facilitate as well as OCE's perspective on balancing inclusivity and efficiency to develop therapeutics that work for all.

2019 FDA Food Safety and Nutrition Survey – Making Food Safety and Nutrition Accessible to Public Health Professionals

Amy Lando, MPP, CFSAN/FDA
Video segment: 1:47:40 – 1:57:32

The Food Safety and Nutrition Survey (FSANS) is FDA's premier, national probability consumer survey designed to assess consumers' awareness, knowledge, understanding, and self-reported behaviors relating to a variety of food safety and nutrition-related topics. The survey findings are intended to help FDA make better informed regulatory, policy, education, and other risk-management decisions aimed at promoting and protecting public health. The survey population is adults (18 years and older) in the 50 U.S. states and the District of Columbia. A total of 4,398 responses were collected during October and November 2019. Ms. Lando discusses motivation for conducting the survey, methods, topics covered in the survey (shopping, preparing, eating,

storing), key findings, and offers resources for additional information on methodology and results.

Advancing Health Equity through Outreach and Communications

Jovonni Spinner, DrPH, MPH, CHES, OMHHE/FDA
Video segment: 1:57:44 – 2:08:28

Health disparities continue to exist in this country for racial and ethnic minority, tribal, and other under-represented groups. COVID 19 has further exposed these disparities. To address these disparities, FDA's Office of Minority Health and Health Equity (OMHHE) uses culturally and linguistically tailored strategies to raise awareness around these concerns. OMHHE's Outreach and Communication Program (OCP) aims to 1) drive improvements in FDA's outreach to minority communities and 2) strengthen awareness of FDA's role in public health, and 3) promote and facilitate engagement between diverse groups and FDA. OCP uses digital and print media as well as interpersonal interactions to reach diverse audiences with information on key health and regulatory issues affecting diverse groups. All communications have an emphasis on addressing cultural competency and low literacy needs. For example, OCP has developed multi-media health education campaigns to address clinical trial diversity that has reached millions through videos, podcasts, and social media; held public meetings on opioids, diabetes, and rural health; disseminated thousands of health education materials for community outreach; implemented staff trainings on cultural competency and bias; and built partnerships with stakeholders to extend our reach. We are committed to addressing health disparities by ensuring diverse groups have credible health information they can act on. Success has been evidenced by deepened stakeholder engagement and increased dialogue around clinical trial diversity, materials requests, and downloads.

Closing Remarks / Discussion

Christine Lee, PharmD, PhD, OMHHE/FDA
Video segment: 2:08:33 – 2:10:55

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Session Chair/Moderator: Suzanne Fitzpatrick, PhD, Senior Advisor for Toxicology, CFSAN/FDA

Introduction: Dr. Suzanne Fitzpatrick, PhD, CFSAN/FDA
Video segment: 0:00 – 0:22

21st Century Solutions for 21st Century Problems

Geoffrey Ling, MD, CEO, On Demand Pharmaceuticals
Video segment: 00:23 – 27:47

On Demand Pharmaceuticals is developing the Pharmacy on Demand (PoD) manufacturing unit to make key starting materials, active pharmaceutical ingredients, and final formulated medicines. PoD is a transportable, miniaturized manufacturing unit designed to manufacture medicine on demand. It can be reconfigured from manufacturing one type of drug to another in a couple of hours and operated in extreme environments with minimal training. PoD is designed to improve access for members of the U.S. military who may be stationed in areas with limited resources as well as populations living in underserved urban communities, rural areas, and tribal territories.

MALDI Imaging Mass Spectrometry: A New Imaging Modality for Use in Toxicological Studies

E. Ellen Jones, PhD, Fellow, NCTR/FDA
Video segment: 28:00 – 43:36

Matrix-assisted laser desorption ionization (MALDI) imaging mass spectrometry (IMS) is an emerging technique that produces 2D ion density maps representing the distribution of an analyte(s) across a tissue section in relation to tissue histopathology. MALDI IMS was initially developed to spatially profile proteins and peptides, however, the variety of detectable analytes (e.g., neurotransmitters and small-molecule drugs) has greatly increased due to advancements in instrumentation and software. Unlike some other imaging modalities, within a single imaging run, MALDI IMS can determine the spatial distribution of a drug, its metabolites, and other endogenous compounds without the need for a label or a priori knowledge. Within drug-centric studies, this approach has potential to further understanding of mechanisms of disease initiation and progression, drug distribution, pharmacology, and toxicology by providing snapshots of temporal and causal changes. This presentation focuses on using MALDI IMS to better understand drug tissue distribution and gain insights into correlated toxicities. Dr. Jones presents case studies assessing pharmacology and PK/PD effects on drug development along with ongoing toxicology studies within the FDA at NCTR.

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Advancing New Alternative Methodologies at FDA: The Expanded Decision Tree

Szabina Stice, PhD, Toxicologist, CFSAN/FDA
Video segment: 44:00 – 58:35

FDA scientists have been taking steps to upgrade FDA's toxicology toolbox to expand its toxicology predictive capabilities for chemicals and mixtures, provide safe intake levels, and reduce the use of animal testing. Among FDA's potential tools to achieve these goals is the Expanded Decision Tree that is based on the Cramer et al. (1978) Decision Tree that sorts and prioritizes substances according to their relative chronic oral toxic potential. The Expanded Decision Tree builds on the Cramer model by using mode of action information; a newly created database composed of toxicity, metabolism, and other data for over 1,900 substances; and more specific questions. This expansion enables improved separation of classes of relative toxic potential, allows the doubling of the number of classes, and results in a broader chemical applicability domain. The Expanded Decision Tree is suitable as a screening and prioritization tool in the safety evaluation of substances with low exposures as well as in the safety assessment of mixtures.

ISTAND: A Pilot Program to Address Novel Technologies as Drug Development Tools (DDTs)

Chris Leptak, MD, PhD, Director, Biomarker Qualification Program, CDER/FDA
Video segment: 58:50 – 1:12:09

Innovative Science and Technology Approaches for New Drugs (ISTAND) is an FDA/CDER pilot program designed to accelerate use of novel drug development tools through Agency-wide coordination, effective communication, and efficient regulatory review. The vision is to enable timely incorporation of innovative science and technology approaches into drug development to benefit public health. ISTAND biomarkers are frequently used by different stakeholder communities. Regulators use them to aid in drug development, including incorporation for specific uses in clinical trials. Dr. Leptak introduces:

- Biomarkers, Endpoints, and Other Tools (BEST) resource
- Components of a biomarker development effort
- Pathways for introduction of biomarker information
- Qualification of biomarkers as Drug Development Tools (DDTs)
- Resources related to biomarkers used as surrogate endpoints

Medical Device Cybersecurity

The 2021 FDA Science Forum: Science as the Foundation for Protecting and Promoting Public Health

Kevin Fu, MEng, PhD, Acting Director of Medical Device Cybersecurity, CDRH/FDA; Associate Professor, University of Michigan
Video segment: 1:12:16 – 1:29:30

Today, it would be difficult to find medical device technology that does not critically depend on computer software. Network connectivity and wireless communication have transformed the delivery of patient care. The technology often enables patients to lead more normal and healthy lives. However, medical devices that rely on software (e.g., drug infusion pumps, linear accelerators, pacemakers) also inherit cybersecurity risks endemic to computing. What's special about medical devices and cybersecurity? How are international standards bodies and regulatory cybersecurity requirements changing the global manufacture of medical devices? This talk provides a glimpse into the risks, benefits, and regulatory issues for medical device cybersecurity, including the importance of effective threat modeling, and innovation of trustworthy medical device software.

FDA's Advanced Manufacturing Journey

Sau (Larry) Lee, PhD, Deputy Director of Science, Chair, Emerging Technology Program, CDER/FDA
Video segment: 1:29:35 – 1:45:00

FDA is undertaking a new approach by working closely with drug makers and other relevant stakeholders to ensure that cutting-edge, scientifically sound methods are used in drug manufacturing (including biotechnology and small-molecule products). The new FDA approach aims to help the pharmaceutical industry adopt novel technologies in producing medicines that are consistently safe and effective. The new approach emphasizes use of (1) FDA's Emerging Technology Program to provide opportunities for early FDA-industry interactions during technology development, (2) regulatory science and research to enhance scientific understanding of novel technologies and support risk assessments, and (3) close collaborations and coordination with other regulatory agencies to support harmonization of scientific and regulatory approaches or standards.

Understanding Ex Vivo Manufacturing of HSC-Based Therapeutics

Pankaj K. Mandal, PhD, Senior Staff Fellow, CBER/FDA
Video segment: 1:45:30 – 1:59:14

Hematopoietic stem cell (HSC)-based cellular therapeutics hold great promise for treatment of hematological disorders, such as hemoglobinopathies, primary immune deficiencies,

lysosomal storage, and metabolic disorders, and congenital cytopenia. Despite significant advances in the development of HSC-based therapies over the past decade, the lack of optimized protocols for HSC expansion ex vivo has delayed their widespread use. FDA/CBER's research program focuses on understanding advanced manufacturing of genome-edited HSC-based therapeutics with the goal of identifying and defining optimal conditions for cost-effective, large-scale manufacturing of genome-edited, HSC-based therapeutics.

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Science Forum Summaries
Session 5: Advancing Products Based on Novel Technologies

Session Chairs/Moderators: Beverly D. Lyn-Cook, PhD, Senior Interdisciplinary Research Biologist, NCTR/FDA; Silvia A. Piñeiro, PhD, Senior Regulatory Review Scientist, CVM/FDA
Video segment: 2:25 – 3:36

Introduction: Sharron Watson, Office of the Chief Scientist, OC/FDA; and Beverly Lyn-Cook, PhD, NCTR/FDA
Video segment: 0:00 – 3:36

Overcoming Challenges in Co-culture of Super Strict Anaerobes with a Healthy Human Colon Mucosal Barrier
Linda G. Griffith, PhD Professor of Biological and Mechanical Engineering, MIT
Video segment: 3:37 – 33:36

The relative lack of technologies for long-term co-culture of a human colonic mucosal barrier with super oxygen-sensitive commensal microbes hinders the study of human-microbe interactions. This talk describes interactions between an abundant super oxygen-sensitive commensal anaerobe, Faecalibacterium prausnitzii, with a primary human mucosal barrier, using a gut-microbiome (GuMI) physiome platform. The investigators designed and fabricated the platform to host the strictest anaerobes and pathogens in continuous culture with a healthy mucosal barrier. The platform provides continuous nourishment of the microbes while simultaneously maintaining delivery of fresh oxygenated medium to the basal side of the

epithelial cells. Long-term continuous co-culture of F. prausnitzii for 2 days with colon epithelia resulted in a strictly anaerobic apical environment fostering growth of and butyrate production by F. prausnitzii while maintaining a stable colon epithelial barrier. The effects of bacterial coculture on the state of the epithelium are consistent with some clinical observations regarding F. prausnitzii, motivating further studies using this platform. The investigators are addressing study limitations by making adaptations to the platform/matrix.

Advancing Regulatory Science Through Organ on a Chip

Daniel A. Tadesse, DVM, PhD Research Microbiologist, Office of Research, CVM/FDA
Video segment: 34:07 – 44:00

The effects of drug residues in or on animal-derived foods on the human intestinal microbiome (disruption of the bacterial colonization barrier and development of antimicrobial resistance) is an important human food safety concern that needs to be addressed during pre-approval evaluations of drug products intended for use in food-producing animals. Animal models, culture models, and static in vitro-transformed cell lines have been used to predict the effects of drug residues on disruption of the bacterial colonization barrier and development of antimicrobial resistance among bacteria resident in the human colon. Recent advances in microphysiological systems present an opportunity to study organ-microbiome-drug interactions by recreating the structure and function of a human organ in vitro that mimics human intestinal physiology and microbial complexity. The investigators are exploring the potential of an intestine-on-a-chip model as an alternative method to study the effects of drug residues on human intestinal microbiome and development of antimicrobial resistance. A validated intestine-on-a-chip model would provide a new and powerful tool for drug sponsors and FDA to address the effects of antimicrobial animal drug residues on human intestinal flora and represents a substantial step forward in FDA's efforts to reduce reliance on animals for research.

Microbiome as an Additional Criterion for Safety Assessment

Sangeeta Khare, PhD Research Microbiologist, NCTR/FDA
Video segment: 44:11 – 55:25

The intestinal microbiome is a key contributor in the metabolism of drugs, food additives, pesticides, herbicides, and other contaminants, collectively known as xenobiotics. However, the commensal microbiome itself could also be impacted by xenobiotics. An in-depth understanding of the experimental model, dose, route, and frequency of exposure is required when evaluating the safety of xenobiotics to which humans are exposed daily. Moreover, there is a need to establish a non-animal model of the gastrointestinal tract (GIT) to address

knowledge gaps related to the interaction of the xenobiotic with the host and microbiome. The aim of this research is to determine novel risk assessment criteria for gastrointestinal toxicity. Interactions of these products with the GIT may have an adverse effect on the commensal microbiota, affect antimicrobial resistance, and alter the host xenobiotic metabolism, immune responses, and intestinal permeability. This presentation discusses current approaches, challenges, and opportunities to establish science-based minimum standards for conducting hazard analyses of such products using different models. The research provides insight into the mechanistic interaction of the xenobiotics-host-microbiome to determine end points to be included in the decision tree for the risk assessment of such products. The presenter provides an example of the interaction of a xenobiotic with the host using innovative methods of risk assessment that could lead to the discovery of biomarkers, improved food safety, and personalized treatment.

Emergence of Nosocomial Associated Opportunistic Pathogens in the Gut Microbiome After Antibiotic Treatment Revealed by a Mouse Model Metagenome Analysis

Zhihua Li, PhD, Biologist, CDER/FDA
Video segment: 55:34 – 1:07:37

According to the Centers for Disease Control and Prevention's 2015 Healthcare-Associated Infection and Antibiotic Use Prevalence Survey, 1 in 31 hospital patients was infected with at least one nosocomial pathogen while being treated for unrelated issues. Many studies associate antibiotic administration with nosocomial infection occurrence. However, there appears to be little direct evidence of antibiotic administration selecting for nosocomial opportunistic pathogens. This study aims to confirm gut microbiota shifts in an animal model of antibiotic treatment to determine whether antibiotic use favors pathogenic bacteria. The investigators found that an antibiotic therapy decreased the number of detectable species of bacteria by at least 20-fold. The gut microbiota of antibiotic-treated mice had a significant increase in opportunistic pathogens that have been implicated in nosocomial infections. Antibiotic treatment selected for antibiotic-resistant gene-enriched subpopulations for many opportunistic pathogens. The authors concluded that oral antibiotic therapy may select for common opportunistic pathogens responsible for nosocomial infections. In this study, opportunistic pathogens pathogens present after antibiotic therapy harbored more antibiotic-resistant genes than populations of opportunistic pathogens before treatment.

Safety and Effectiveness of Fecal Microbiota for Transplantation Products

Paul Carlson, PhD Principal Investigator, Office of Vaccines Research & Review, CBER/FDA

Video segment: 1:08:00 – 1:19:15

Fecal Microbiota for Transplantation (FMT) has become a therapy of interest for a wide range of indications from colonization resistance against bacterial pathogens to inflammatory conditions and even metabolic and neurological disorders. The most well-studied indication for FMT is the treatment of recurrent Clostridioides difficile infections (CDI), with some studies reporting >90 percent efficacy. From a regulatory perspective, FMT presents unique challenges. Since the "active ingredient" in these drugs is currently unknown and likely different for each indication FMT is intended to treat, it is difficult to develop the types of assays and tools that would facilitate an understanding of important product characteristics. An increased understanding of the mechanisms controlling effective FMT could aid researchers and FDA in understanding these processes and facilitate product development in this arena. This research seeks to advance our understanding of FMT safety (donor screening, including the risk of SARS-CoV-2), manufacturing (how do manufacturing methods/ conditions alter microbiome composition), and effectiveness (identification of markers important for potency).

Microphysiological System Regulatory Research Considerations: Evaluation of a Model System

Kirsten Eckstrum, PhD, Research Biologist, CFSAN/FDA
Video segment: 1:19:26 – 1:33:15

Microphysiological systems (MPS) or organ-on-a-chip models employ the use of multiple cell types and flow of media to mimic physiological stimuli. With the use of human cells, these systems have the potential to become more predictive tools for drug safety and toxicity testing than current animal models. To assess the usefulness of these systems in determining toxicity the authors examined one such platform, the Emulate two-cell Liver-Chip, which used primary human hepatocytes and liver sinusoidal endothelial cells (LSECs). They explored the necessary components and considerations for Liver-Chip studies; predictivity, sensitivity, and specificity, power or sample size requirement; and variability within the system using eight compounds of known hepatotoxic potential. Findings demonstrated that Liver-Chip studies could easily be performed in a regulatory testing environment with proper SOPs in place, including proper analysis of chemical-chip interaction. For the compounds tested, the Liver-Chip model accurately predicted toxicity with most tested compounds; sensitivity and specificity were high, Liver-Chips needed a sample size of three to four chips, and variability was low both within and between experiments. The results suggest that MPS could be useful for regulatory research. Further studies are needed to fully understand the usefulness of the platform.

Evaluation of Endothelial Cell Responses to Nanomaterials Using a Dynamic Flow Model

Shelby Skoog, PhD, Biomedical Engineer, CDRH/FDA
Video segment: 1:33:32 – 1:43:40

With expanding applications of nanomaterials in innovative drugs and medical devices, there is a need for improved test methods to evaluate their safety before clinical use. Traditional in vitro biological evaluation approaches do not account for the complex interactions of nanomaterials with the physiological environment. Furthermore, in vivo animal studies are expensive, time-consuming, may not reflect human responses, and include ethical considerations for use of animals. Advanced in vitro test methods, such as organ-on-a-chip microphysiological systems (MPS), have demonstrated potential in toxicological research by providing a more physiologically relevant environment. These dynamic, in vitro models using human cells may help bridge the gaps between traditional in vitro cell studies and in vivo animal evaluation and better predict clinical responses when assessing safety of medical products containing nanotechnology. Because nanomaterials are being increasingly used in medical devices and drugs using intravascular administration, the investigators' preliminary research focused on using an endothelium-on-a-chip fluidic model to evaluate biological responses to nanoparticles under shear flow conditions similar to human vasculature. They evaluated the effects of silver nanoparticles on human cerebral microvascular endothelial cells under dynamic flow conditions compared to static conditions. The results demonstrate that dynamic flow conditions affect the nanomaterial aggregation, and the endothelial cell responses to the nanoparticles depends on the nanomaterial concentration and the experimental flow conditions (e.g., dynamic vs. static). This study highlights the impact of physiologically relevant environment in safety evaluation of nanomaterials.

Microphysiological Systems to Assess the Functional Capacity of Regenerative Medicine Cellular Products

Kyung Sung, PhD, Principal Investigator, CBER/FDA
Video segment: 1:43:55 – 1:53:58

As described in the 21st Century Cures Act, products eligible for Regenerative Medicine Advanced Therapy (RMAT) designation include cellular therapies, therapeutic tissue-engineered products, human cell and tissue products, or any combination products that use such therapies or products. Multipotent stromal cells (MSCs) and induced Pluripotent Stem Cells (iPSCs) have been popular sources for manufacturing RMAT products due to their ability to undergo lineage-specific differentiation. For successful clinical translation of such cell-based products, there is a paucity of reliable markers that can predict the products' in vivo performance. For instance, MSCs are heterogeneous and responsive to their surrounding environment, resulting in distinct subpopulations of cells with potentially different qualities needed for product potency. Because

there are numerous biochemical and biomechanical factors regulating the functions of MSCs, it is critical to develop reliable high-throughput assays that enable the efficient exploration of large and complex parameters for evaluating cellular function. Microphysiological systems offer the practicality to fulfill this unmet need. Several simple microfluidic channel arrays have been successfully implemented in screening the influence of paracrine mediators and various tissue microenvironment components in the regulation of cellular functions. Further, microphysiological three-dimensional organoids and tissue-like structures, such as chondrogenic cell aggregates and blood vessels have been incorporated into high-throughput, cell-based screening platforms in efforts to provide functionally relevant conditions. This presentation gives an overview of practical microscale technologies that are simple to operate while enhancing throughput, relevance, and reliability. The presenter discusses how such technologies could be employed in assessing cell-based products.

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

Session Chair: Carol Weiss, MD, PhD, CBER/FDA

Introduction: Dr. Carol Weiss, CBER/FDA
Video segment: 3:00 – 3:26

Outbreak Preemption and Response in the Genomic and Information Age
Pardis Sabeti, MD, PhD, Professor, Broad Institute
Video segment: 3:30 – 29:40

Just as the COVID-19 crisis has emphasized the critical importance of rapidly detecting and containing pathogens, we are on the cusp of a new era in infectious disease surveillance and response. Ultra-sensitive genomic technologies can detect pathogens and be developed into affordable point-of-care diagnostics to be deployed anywhere. Cloud-based information systems allow us to continuously collect, integrate and share viral surveillance data to guide public health actions. By unifying these tools into a coherent system, we can detect and prevent

pandemics on the ground before they start. As a global community we need to: rapidly detect infections with genomics-based tests; enable swift, coordinated responses by connecting and empowering frontline healthcare workers, hospitals, laboratories, and public health institutions to share data and analytics; and empower the public health community to stop infectious diseases before they spread. This presentation traces the etiology and spread of Ebola and Zika viruses, describes the workings of the CRISPR systems, and explains how investigations at the single-cell and molecular levels can identify how viruses change within hosts.

Evaluation of Pathogenesis of SARS-CoV-2 Variants

Tony Wang, PhD, Principal Investigator, CBER/FDA
Video segment: 30:00 – 45:05

The outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has quickly turned into a global pandemic. FDA's Center for Biologics Evaluation and Research (CBER) issued emergency use authorization (EUA) to three vaccines, all of which express the viral spike protein as immunogen. SARS-CoV-2 variants of concern have emerged in many parts of the world, some of which show signs of partial escape of immunity elicited by existing vaccines. This presentation covers experimental results on the pathogenesis of SARS-CoV-2 variants, particularly the pathogenesis of the B.1.1.7 variant and resulting implications for designing and conducting vaccine pre-clinical trials.

Intelligence-Powered Drug Repurposing Against COVID-19

Zhichao Liu, PhD, NCTR/FDA
Video segment: 45:20 – 59:50

There is an urgent need to develop a robust framework of safe and effective therapeutic options for COVID-19. Interplay between immune and mitochondria systems plays an essential role in COVID-19 etiology. Dr. Liu proposes a modified DeepFake model framework to unravel the immune and mitochondria continuums for precision medicine-based drug repurposing for this disease. To develop the model, investigators integrated more than 3 million multi-omics data points associated with immune, mitochondria, and drug transcriptomic responses and obtained a list of 21 immune and mitochondria continuums highly associated with the severity and pre-existing conditions of COVID-19 patients. By mapping FDA-approved drugs and investigated compounds onto the obtained immune and mitochondria continuums, they obtained a list of repurposing candidates for COVID-19 patients with different manifestations. The proposed DeepFake model could further uncover the interplay between

immune and mitochondria systems and pave a new way for precision medicine-based drug repurposing against COVID-19.

Device Medical Countermeasure Activities During the COVID-19 Pandemic

Heather Agler, PhD, Senior Program Manager, CDRH/FDA
Video segment: 1:00:06 – 1:15:45

The FDA plays a critical role in emergency preparedness and operations, including during the COVID-19 pandemic response. Many devices such as diagnostic tests, personal protective equipment, ventilators, monitoring devices, and injection devices have played important roles. The response has also emphasized the need for new medical countermeasures. The FDA Center for Devices and Radiological Health's (CDRH's) approach has been to allow regulatory flexibility by issuing emergency use authorizations and immediately-in-effect guidances that allow enforcement discretion for certain devices or capabilities added to existing devices. These policies provide opportunities for manufacturers to create early access to new innovative solutions for better patient care. Having the devices on the market creates opportunities to collect real-world evidence on those devices available during the pandemic. This experience can lead to innovative products that will prepare us for the next event. The COVID-19 pandemic has reinforced the need for a robust and resilient supply chain. CDRH is assessing supply chain weaknesses to determine how best to prevent shortages.

Emerging Technologies for Adventitious Agent Detection and Their Application to CDER Products

Kathryn E King, PhD, Staff Scientist/Product Quality Assessor, CDER/FDA
Video segment: 1:16:00 – 1:30:16

In addition to the infectious agents that are currently the target of novel biotechnology therapies, adventitious agents can impact the manufacture of products. Adventitious agents are microorganisms that are unintentionally introduced into a manufacturing process/drug product. Biotechnology products must be shown to be free from adventitious agent contamination. Contamination events not only pose risk of transmission of pathogenic agents to patients but also can impact drug supply due to the need for event remediation. Traditional routine tests for adventitious agents have relied on culture methods, which are subject to long incubation periods. Novel technologies for detecting adventitious agents have been steadily evolving over time towards more rapid and broader methods designed to detect unanticipated as well as predicted potential contaminants. Some of these technologies can detect microbes that were not detected by traditional methods. Thus, there is enhanced interest in novel testing

methods to ensure biosafety, while cutting down on time to results. This presentation focuses on examples of novel technologies that are being considered or have been accepted for routine use to detect bacteria, mycoplasma, and adventitious viruses. Dr. King discusses considerations for next-generation sequencing as well as available resources and reagents.

ORA's Work in Support of Medical Countermeasures

Elizabeth Miller, PharmD, Assistant Commissioner for Medical Products and Tobacco Operations, ORA/FDA
Video segment: 1:30:33 – 1:47:29

FDA and its component centers routinely collaborate to advance public health through thorough review of submitted applications and on-site regulatory inspections to ensure manufacturing readiness, among other items. The Federal Food, Drug, and Cosmetic Act (FD&C Act) gives FDA authority to grant an emergency use authorization (EUA) for a medical product intended for use in an actual or potential emergency (emergency use). An EUA allows unapproved medical products and approved products with unapproved uses to be introduced into interstate commerce if they may be effective as medical countermeasures during declared public health and other national emergencies and there is no available, approved alternative. Interactions between a sponsor and FDA related to an EUA request may include investigations by FDA of a facility that will manufacture, package, label, or test a medical product subject to an EUA, to inform the Center's decision-making. This presentation provides a high-level overview of the novel regulatory framework during the pandemic, including ORA's efforts to evaluate manufacturing operations for vaccines and therapeutics. Dr. Miller gives examples of real-world impact supporting emergency use authorization, lessons learned from the investigative teams, and emphasizes the importance of having multiple tools available and developing new tools in order to be able to respond effectively and continue operations during a public health emergency.

Panel Discussion

Moderator: Dr. Carol Weiss
Panel: Dr. Heather Agler, Dr. Kathryn King, Dr. Zhichao Liu, Dr. Elizabeth Miller, Dr. Pardis Sabeti, Dr. Tony Wang
Video segment: 1:48:00 – 1:58:46

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Science Forum Summaries
Session 7: Food and Cosmetic Safety: The Role of Innovation and Technology

Session Chairs/Moderators: Chad Nelson, MSPH, PhD, CFSAN/FDA; Jeffrey Ward, DVM, CVM/FDA; Zhichao Lin, PhD, ORA/FDA

Introduction: Chad P. Nelson, MSPH, PhD, CFSAN/FDA
Video segment: 0:00 – 1:44

One Health as a Collaborative Response to Food Safety Risks

Kalmia Kniel, PhD, Professor, Animal and Food Sciences, University of Delaware
Video segment: 1:44 – 24:00

One Health is a scientific perspective that considers human, animal, and environmental health as an integrated whole. The goals of One Health are to reduce disease and optimize health by considering the myriad interactions and connections within the human, animal, and environmental triad. One Health enables a collaborative approach towards solving many of the world's health-related issues and most pressing challenges such as advancing food security and food safety and addressing emerging infectious diseases in the context of ecosystems. We encounter One Health issues every day; this has been emphasized by the ongoing COVID-19 crisis. It is estimated that more than 75 percent of emerging and re-emerging diseases are either zoonotic or vector-borne. One Health issues critical for food safety and food security include Salmonella and avian influenza. The lens of One Health offers an innovative way to consider the interfaces between agricultural practices, nutrition, risk reduction, consumer preferences, and environmental sustainability.

CFSAN's Use of Innovative Science to Address Current and Emerging Public Health Priorities

Susan Mayne, PhD, Director, CFSAN/FDA
Video segment: 24:16 – 37:31

The FDA is a scientific, regulatory agency responsible for the safety of the nation's domestically produced and imported foods, cosmetics, drugs, biologics, medical devices, and radiological products. FDA's Center for Food Safety and Applied Nutrition (CFSAN) conducts regulatory

science-related research to increase our understanding of the underlying factors and variables that may contribute to or pose a risk to human safety and health for CFSAN-regulated products which are human foods, including dietary supplements, as well as cosmetics. In addition to traditional approaches to laboratory science, CFSAN also engages in and encourages development of novel technologies for detecting, reducing, inactivating, or eliminating f hazards from FDA-regulated products. We embrace a variety of innovative scientific methods including: predictive toxicology to inform better decisions while reducing or eliminating the use of animals in toxicity testing; consumer studies in nutrition and labeling as well as food safety to recognize consumer views and understanding in order to provide information that will empower consumers to make the most informed decisions; genomics, metagenomics and bioinformatics to clarify the root cause of foodborne outbreaks, support investigations, and prevent future outbreaks; development of more rapid analytical methods to set the global standards for measuring chemicals of concern, such as cannabidiols (CBD), per- and polyfluoroalkyl substances (PFAS), and metals; and risk assessments to inform policy decisions and prioritization aimed at reducing consumer exposure to potential hazards in food. Dr. Mayne discusses how CFSAN uses innovative science to address current and emerging public health priorities related to FDA-regulated foods, including dietary supplements, as well as cosmetics.

FDA Support of Recent Foodborne Illness Outbreak Investigations

Daniel Rice, MS, DrPH, ORA/FDA
Video segment: 37:50 – 51:25

FDA is a significant partner in the response to outbreaks of foodborne illness associated with most human and animal food products in the United States. FDA's Center for Food Safety and Applied Nutrition (CFSAN) and Center for Veterinary Medicine (CVM), compliance programs, inspection programs, and laboratories collectively work towards outbreak response, surveillance, and post-response activities related to incidents involving illnesses linked to FDA-regulated human and animal food products. Early identification of illness clusters; rapid and effective regulatory response to remove contaminated food from distribution; and targeted outreach activities to inform consumers are instrumental to an effective public health impact. Investigations of multi-state outbreaks of foodborne illness are complex and require coordinated efforts among regulatory and public health partners spanning federal, state, and local government agencies that collectively contribute to identifying outbreaks and mitigating impact on consumers. These agencies coordinate epidemiological investigations, inspections, sampling, and testing and evaluate distribution of implicated products. In recent years, FDA has provided technical, epidemiological, inspectional, and laboratory support for several outbreaks of foodborne illness, including E.coli O157:H7 in leafy greens, Cyclospora cayetanensis in fresh

produce, Salmonella enterica in a variety of products and hepatitis and norovirus in fresh berries and fresh produce. This presentation provides an overview of successes, challenges, and strategies FDA uses to respond to outbreaks of foodborne illnesses and to assess the safety of food consumed in the United States.

What Won't an Animal Eat? Innovation in Animal Diets

David Edwards, PhD, CVM/FDA
Video segment: 51:43 – 1:06:24

Animal food is a $297 billion U.S. market that includes food for livestock, aquaculture, and pets, and affects both animal and human health. Ingredients in these products are becoming more complex. The food that a food-producing animal eats becomes part of our food. And, companion animals are members of our family whose lives we want to be long and healthy. Innovative ingredients continue to be developed for the animal food market. Although animals have always consumed byproducts from production of human food (e.g., extra bakery products not put into the human food supply), newer ingredients derive from partitioning foods into fractions for specific nutritional needs. Other animal food ingredients start out in fermentation tanks, where microbes may produce specific nutrients or be fed as ingredients themselves. FDA recently reviewed the use of oil from single cell algae to serve as an alternative source of docosahexaenoic acid (DHA) for dog food. FDA also reviewed black soldier fly larvae, which are raised on food scraps that would otherwise have gone to waste. The insects are turned into high-quality food for poultry, swine, dogs, and salmon. Animals generally eat a very limited and defined diet as their sole nutrition over their whole lifetime. Reviewing new animal food ingredients enables FDA to evaluate new ingredients for safety and to make sure they function as intended. This helps ensure that people provide optimal nutrition to help keep animals healthy, while also ensuring that the meat, milk, and eggs from animals are safe for people to eat.

Mind the [Data] Gap: Contributions of FDA's NCTR to Evaluate Cosmetics Safety

Luisa Camacho, PhD, NCTR/FDA
Video segment: 1:06:36 – 1:19:35

FDA's NCTR conducts scientific research and develops and evaluates innovative scientific tools to support FDA's regulatory processes. NCTR's research portfolio includes multiple programs designed specifically to address regulatory data gaps on the safety of cosmetics. Examples of studies conducted at NCTR in this context include the microbiological survey of commercial tattoo inks; characterization of the genotoxicity, mutagenicity, and toxicity of ingredients used in skincare and personal care products; and evaluation of the skin permeation profiles of cosmetic ingredients using in vivo and in vitro methods. This presentation gives an overview of

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NCTR's scientific expertise and illustrates how it applies to evaluating multiple aspects of cosmetics safety in support of FDA's mission to protect and promote individual and public health.

Panel Discussion
Moderator: Dr. Jeffrey Ward
Panel: Dr. Luisa Camacho, Dr. David Edwards, Dr. Kalmia Kniel, Dr. Susan Mayne, Dr. Chad P. Nelson, Dr. Daniel Rice
Video segment: 1:20 – 2:00:16

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Science Forum Summaries
Session 8: Substance Use, Misuse, and Addiction

Session Moderators: Marta Sokolowska, PhD, FDA Center for Drug Evaluation and Research

Introduction: Marta Sokolowska, PhD
Video segment: 0:00 – 3:18

Substance Use Disorders Linked to COVID-19 Susceptibility
Nora D. Volkow, MD, Director, National Institute on Drug Abuse/National Institutes of Health
Video segment: 3:20 – 31:05

The misuse of and addiction to opioids—including prescription pain relievers, heroin, and synthetic opioids such as fentanyl—have resulted in a national crisis of overdose deaths. In parallel, an alarming resurgence in stimulant use -- including cocaine and methamphetamine—is further contributing to the rise in overdose fatalities. This crisis is now exacerbated by the COVID-19 pandemic, which has resulted in increased drug use and relapse of some in treatment and highlights the urgency to characterize the unique social and structural challenges faced by those with substance use disorders and to develop strategies to overcome them.

This presentation highlights such challenges as the increased use of fentanyl by itself or in combination with other opioids or stimulant drugs like cocaine and methamphetamine. It also focuses on how NIH researchers are using scientific advances to address the opioid crisis amidst the COVID pandemic, which includes developing new medications and formulations to help treat opioid use disorders and overdoses; prevention strategies to mitigate an individual's vulnerability to addiction; and implementation science to guide optimal deployment of therapeutic interventions including the use of telehealth in diverse settings (e.g., healthcare, justice setting, and rural communities).

COVID-19 and the Opioid Crisis: A Social Media Perspective

Jill Settle, PhD, FDA Center for Drug Evaluation and Research
Video segment: 31:31 – 45:59

Negative outcomes at the intersection of the opioid crisis and the COVID-19 pandemic are evident, including increased substance use, decreased treatment seeking, and rising overdoses. However, little is currently known about how those affected by opioid abuse and addiction feel about these or other aspects of the pandemic. To that end, the investigators conducted an in-depth, systematic, exploratory qualitative analysis of 1,623 online and social media posts that included personal experiences with the pandemic and opioid abuse and addiction from the early months of the pandemic, between March 1 and April 30, 2020. Social media research permits collection of the personal perspectives and experiences of a large and heterogeneous group of people, enabling discovery of broad and detailed information without the practical limitations of other types of research. The analyses identified unexpected findings as well as contributed to a broader understanding of how affected individuals are handling the intersection of these public health crises.

And the Kids Vaped On: Teens, Tobacco, and the National Youth Tobacco Survey

Karen Cullen, PhD, MPH, FDA Center for Tobacco Products
Video segment: 47:07 – 1:03:30

Most tobacco-use behaviors are initiated during youth and young adulthood; nearly 9 in 10 U.S. adult cigarette smokers first try smoking by age 18. E-cigarette use has increased considerably among youth since 2011; according to data from the National Youth Tobacco Survey (NYTS), e-cigarettes have been the most commonly used tobacco product among youth since 2014. The alarming increase in current (past 30-day) use of e-cigarettes by middle and high school students between 2017 and 2018 reversed the declines in youth use of any tobacco

observed in prior years. In 2019, NYTS data showed that current e-cigarette use remained high, while current cigarette smoking among high school students declined to historic lows.

School closures from the COVID-19 pandemic meant data collection for the 2020 NYTS ended early. Based on data collected from January to March 2020, 23.6 percent of high school and 6.7 percent of middle school students reported current tobacco product use, with 19.6 percent of high school and 4.7 percent of middle school students reporting current e-cigarette use. Cigarette smoking among youth remained at historic lows—4.6 percent of high school and 1.6 percent of middle school students reported smoking cigarettes in 2020. Ongoing surveillance of tobacco product use is critical to inform evidence-based public health policy, planning, and practice to reduce the initiation and use of all forms of tobacco products among U.S. youth. The presenters examine data on youth tobacco product use from the NYTS and discuss recent policies implemented in response to the high levels of youth tobacco use.

Investigation of Opioid Exposure and Neural Tube Defects – In Vivo and In Vitro Approaches

Amy Inselman, PhD, FDA Center for Toxicological Research
Video segment: 1:03:31 – 1:21:44

Opioid exposure during early pregnancy has been associated with an increased risk of neural tube defects (NTDs). Limitations with previous epidemiological study designs, conflicting results from human and animal studies, and incomplete maternal toxicity data have complicated risk assessment for the drug class. To better understand the risks of early pregnancy exposures, in vivo and in vitro approaches are being employed to address existing data gaps. In vivo studies have focused on maternal toxicity, specifically hypoxia, on neural tube development. CF-1 mice were given a single injection of morphine, methadone or the positive control valproic acid on gestational day (GD) 8 of pregnancy. Changes in uterine artery blood flow and statistically significant changes in blood gas parameters, suggestive of maternal hypoxia, were observed following opioid administration. Teratological assessments found the highest incidence of NTDs in fetuses exposed to the higher levels of morphine. In vitro studies have examined direct opioid exposure on differentiating neural precursor cells. Neural precursor cells, derived from human-induced pluripotent stem cells, were treated with various concentrations of opioids during embryoid body formation and assessed for their ability to form neural rosettes, a surrogate endpoint for neural tube development. Preliminary results indicate little effect of opioid exposure on cell proliferation or neural rosette formation. Together, the two lines of investigation may help to address the current data gaps and provide useful supplemental data regarding opioid risks during pregnancy.

Tobacco and Cannabis – Did EVALI Teach Us Anything?

The 2021 FDA Science Forum: Science as the Foundation for Protecting and Promoting Public Health

Priscilla Callahan-Lyon, MD, FDA Center for Tobacco Products
Video segment: 1:22:00 – 1:37:35

In late summer of 2019, healthcare providers across the country began noticing a disturbing trend of youth and young adults with a serious respiratory illness requiring aggressive medical treatment. The common factor was use of aerosolized (or vaping) products – usually identified with nicotine-containing electronic cigarettes. As the E-cigarette or Vaping product use Associated Lung Injury (EVALI) investigation moved forward, the association with cannabis products was recognized. The coordinated taskforce investigation conducted by the Centers for Disease Control and Prevention, FDA, and state health officials identified Vitamin E Acetate as a likely causative agent for many of the described cases. In addition, it was also noted that many of the EVALI patients used multiple products and there was significant overlap in the populations of nicotine and cannabis users. Data from multiple other studies demonstrate the extent of the dual use problem. There are health effects and other concerns associated with use of each type of product that may be accentuated when individuals use both product types. The scientific community should collaborate on work to reduce nicotine and cannabis use as the user populations have significant overlap.

Panel Discussion
Moderator: Dr. Marta Sokolowska, Dr. Nora Volkow, Dr. Jill Settle, Dr. Karen Cullen, Dr. Amy Inselman, Dr. Priscilla Callahan-Lyon
Video segment: 1:37:50 – 1:58:28

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